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GROUP 120

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 4278689
Issued July 14, 1981

Inventors: Keith C. Murdock
Frederick E. Durr

Assignee: AMERICAN CYANAMID COMPANY, One Cyanamid
Plaza, Wayne, New Jersey 07470

Title: 1,4-Bis(Substituted-Amino)-5,8-Dihydroxy-
anthraquinones and Leuco Bases Thereof

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

SIR:

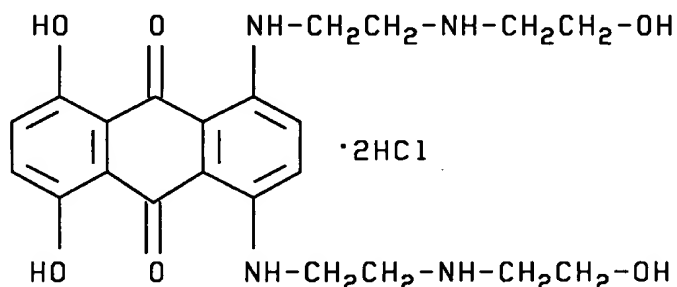
APPLICATION FOR EXTENSION
OF PATENT TERM

This application, filed in duplicate, is respectfully submitted pursuant to the provisions of 35 U.S. Code 156, Extension of Patent Term. It is hereby certified that the duplicate application is identical to this original application. An extension of the term of U.S. Patent No. 4278689 claiming compositions containing the "approved product" (as defined hereinafter) is respectfully requested.

Applicant has determined and submits that U.S. Patent No. 4278689 is subject to, and meets the conditions for, extension of its term in compliance with the GUIDELINES FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156, published in 1047 OG 16-20 (1984), section A paragraphs (a)-(b) and section B paragraphs (a)-(g) thereof, and that this application for extension of patent term is being submitted in compliance with section C thereof.

The following paragraph numbers correspond to those in the GUIDELINES FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156, section D paragraph (b) thereof:

(1) The approved product is 1,4-bis[2-(2-hydroxy-ethylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride which may be represented by the following structural formula:



in association with a pharmaceutical carrier. The approved product is an antineoplastic agent which is marketed abroad under the generic name mitoxantrone hydrochloride and the trade name Novantrone®.

(2) The Federal statute under which the regulatory review occurred is the Federal Food, Drug, and Cosmetic Act (June 25, 1938, ch. 675, §505, 52 Stat. 1052).

(3) The approved product, identified in paragraph (1) above, received permission for commercial marketing on December 23, 1987.

(4) This application is being submitted within the sixty day period permitted for submission under 35 U.S.C. 156. The last day on which the application could be submitted is February 20, 1988.

(5) The patent for which an extension is being sought is U.S. Patent No. 4278689, issued July 14, 1981 to inventors Keith C. Murdock and Frederick E. Durr.

(6) A copy of the patent for which an extension is being sought, in single column form, is attached to this application and is identified as Exhibit A.

(7) A copy of the only certificate of correction filed in U.S. Patent No. 4278689 is attached to this application and is identified as Exhibit B. No disclaimer has been filed in this patent. No maintenance fees are due on this patent since it is based on an application filed prior to December 12, 1980 (37 CFR 1.20). No reexamination certificate has issued in this patent. The assignee of record has not filed a request for reexamination and has no knowledge of any third party filing such a request.

(8) Claims 1, 3, 12 and 18 of U.S. Patent No. 4278689 claim pharmaceutical compositions wherein the approved product is either specifically or generically recited as the active ingredient therein. The approved product is within the scope of the definition of the active ingredient in Claims 1, 3 and 18 whereas Claim 12 specifically recites the approved product as the active ingredient.

(9) The relevant dates and information pursuant to 35 U.S.C. 156(g) are:

April 16, 1979 - effective date of investigational exemption for a new drug under §505(i)-hereafter IND No. 16-332.

May 18, 1984 - effective date of new drug application under §505(b)-hereafter NDA No. 19-297.

Dec. 23, 1987 - effective date of approval of NDA No. 19-297.

(10) A brief description of the activities undertaken by the assignee of record of U.S. Patent No. 4278689 during the regulatory review period with

respect to the approved product is attached to this application and is identified as Exhibit C.

(11) In the opinion of the applicant, U.S. Patent No. 4278689 is eligible for an extension of its term of two years. The length of extension was determined as follows:

(a) The period of IND No. 16-332; which is the period beginning on the issue date of the patent and ending on the filing date of NDA No. 19-297 which is from July 14, 1981 to May 18, 1984; is 1,040 days.

(b) The period of NDA No. 19-297; which is the period beginning on the date the application was initially submitted and ending on the date such application was approved which is from May 18, 1984 to December 23, 1987; is 1,315 days.

(c) Pursuant to 35 U.S.C. 156(c), the period of extension equals one-half the period of IND No. 16-332 plus the period of NDA No. 19-297 which is $1,040/2 + 1,315$ which is 1,835 days.

(d) HOWEVER: U.S. Patent No. 4278689 issued before the date of enactment of 35 U.S.C. 156, and a request for an exemption described in 35 U.S.C. 156(g)(1)(B) with respect to the approved product was submitted before such date of enactment, and the commercial marketing or use of the product had not been approved before such date of enactment. Therefore, the period of extension pursuant to 35 U.S.C. 156(g)(4)(C) may not exceed two years.

(12) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to this application for extension of patent term. Inquiries for such information may be

directed to Messrs. R.P. Raymond (203)348-7331 (Ext. 2672) or E.A. Conroy (203)348-7331 (Ext. 2249).

(13) The Commissioner is hereby authorized to charge Applicant's Deposit Account No. 01-1300 for the prescribed fees for receiving and acting upon this application for extension of patent term and the declaration submitted therewith.

The declaration pursuant to section D paragraph (c) of the GUIDELINES FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 is attached to this application and is identified as Exhibit D.

It is then respectfully submitted that this application is complete and in order and that U.S. Patent No. 4278689 is entitled to an extension of its term of two years and such action is earnestly solicited.

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February 16, 1988

EAC/jhr
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EXHIBIT A

United States Patent [19]

Murdock et al.

[54] 1,4-BIS(SUBSTITUTED-AMINO)-5,8-DIHYDROXY-ANTHRAQUINONES AND LEUCO BASES THEREOF

[75] Inventors: Keith C. Murdock, Pearl River, N.Y.;
Frederick E. Durr, Ridgewood, N.J.

[73] Assignee: American Cyanamid Company,
Stamford, Conn.

[21] Appl. No.: 63,285

[22] Filed: Aug. 2, 1979

Related U.S. Application Data

[60] Division of Ser. No. 923,602, Jul. 11, 1978, Pat. No. 4,197,249, which is a continuation-in-part of Ser. No. 873,040, Jan. 30, 1978, abandoned, which is a continuation-in-part of Ser. No. 824,872, Aug. 15, 1977, abandoned.

[51] Int. Cl.³ A61K 31/135

[11] 4,278,689

[45] Jul. 14, 1981

[52] U.S. Cl. 424/330

[58] Field of Search 424/330

[56] References Cited

U.S. PATENT DOCUMENTS

3,646,072 2/1972 Shaw 260/380

OTHER PUBLICATIONS

Chemical Abstracts 88:83369t (1978).

Primary Examiner—Jerome D. Goldberg

Attorney, Agent, or Firm—Edward A. Conroy, Jr.

[57] ABSTRACT

This disclosure describes symmetrical 1,4-bis(substituted-amino)-5,8-dihydroxyanthraquinones useful as chelating agents and for inhibiting the growth of transplanted mouse tumors.

29 Claims, No Drawings

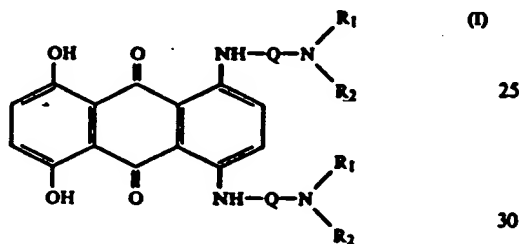
**1,4-BIS(SUBSTITUTED-AMINO)-5,8-DIHYDROXY-
ANTHRAQUINONES AND LEUCO BASES
THEREOF**

**CROSS REFERENCE TO RELATED
APPLICATION**

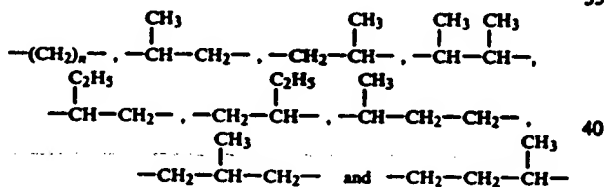
This application is a division of application Ser. No. 923,602, filed July 11, 1978, now U.S. Pat. No. 4,197,249 which is a continuation-in-part of our copending application Ser. No. 873,040, filed Jan. 30, 1978 now abandoned, which is a continuation-in-part of our abandoned application Ser. No. 824,872, filed Aug. 15, 1977.

BRIEF SUMMARY OF THE INVENTION

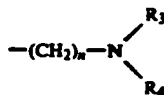
This invention relates to new organic compounds and, more particularly, is concerned with novel symmetrical 1,4-bis(substituted-amino)-5,8-dihydroxyanthraquinones which may be represented by the following general formula:



wherein Q is a divalent moiety selected from the group consisting of those of the formulae:



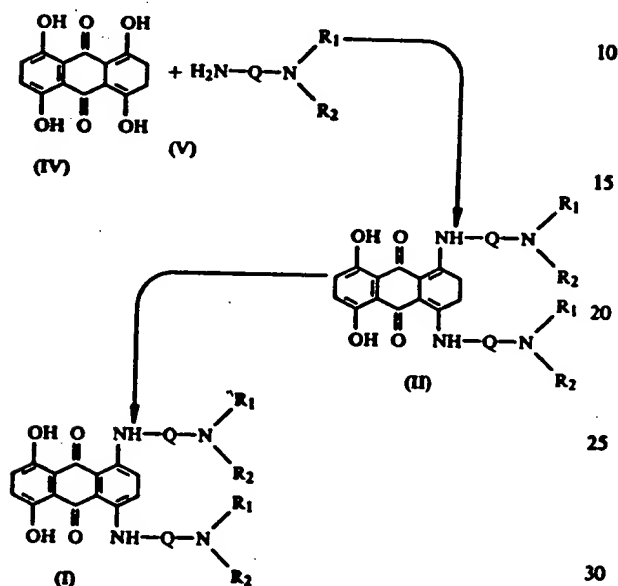
wherein n is an integer from 2 to 4, inclusive; R₁ and R₂ are each individually selected from the group consisting of hydrogen, alkyl from 1 to 4 carbon atoms, monohydroxyalkyl having from 2 to 4 carbon atoms and wherein the carbon atom alpha to the nitrogen atom may not bear an hydroxy group, dihydroxyalkyl having from 3 to 6 carbon atoms and wherein the carbon atom alpha to the nitrogen atom may not bear an hydroxy group, formyl, alkanoyl having from 2 to 4 carbon atoms, trifluoroacetyl and moieties of the formulae: --- (CH₂)_n---CN, --- (CH₂)_n---O---R and



wherein n is an integer from 2 to 4, inclusive, R is alkyl having from 1 to 4 carbon atoms, and R₃ and R₄ are each individually selected from the group consisting of hydrogen, alkyl having from 1 to 4 carbon atoms, and monohydroxyalkyl having from 2 to 4 carbon atoms and wherein the carbon atom alpha to the nitrogen atom may not bear an hydroxy group, and R₃ and R₄ taken together with their associated N(itrogen) is morpholino,

crystalline solids, relatively soluble in water, methanol and ethanol but relatively insoluble in non-polar organic solvents such as diethyl ether, benzene, toluene, and the like.

The novel compounds of the present invention may be readily prepared in accordance with the following reaction scheme:



wherein R_1 , R_2 and Q are as hereinabove defined. In accordance with this reaction scheme, leuco 1,4,5,8-tetrahydroxyanthraquinone (IV) is condensed with an appropriate alkylene diamine (V) in a solvent such as N,N,N',N''-tetremethylethylenediamine, methanol, ethanol, water, dimethylformamide, or mixtures thereof at from about 40° C. to about 60° C. under an atmosphere of nitrogen for several hours to produce the corresponding leuco bases (II). The leuco bases (II) may be readily oxidized to the fully aromatic derivatives (I) by a variety of methods such as air oxidation or treatment

with hot nitrobenzene, or treatment with chloranil, hydrogen peroxide, or sodium perborate.

- The novel compounds described herein are useful as chelating, complexing or sequestering agents. The complexes formed with polyvalent metal ions are particularly stable and usually soluble in various organic solvents. These properties, of course, render them useful for a variety of purposes wherein metal ion contamination presents a problem; e.g., as stabilizers in various organic systems such as saturated and unsaturated lubricating oils and hydrocarbons, fatty acids and waxes, wherein transition metal ion contamination accelerates oxidative deterioration and color formation. They are further useful in analyses of polyvalent metal ions which may be complexed or extracted by these materials and as metal carriers. Other uses common to sequestering agents are also apparent for these compounds. In addition, the leuco bases (II) are useful as intermediate in the preparation of the fully aromatic derivatives (I).
- The novel compounds of the present invention also possess the property of inhibiting the growth of transplanted mouse tumors as established by the following tests.

Lymphocytic leukemia P388 test

- The animals used are DBA/2 mice all of one sex, weighing a minimum of 17 g. and all within a 3 gram weight range. There are 5 or 6 animals per test group. The tumor transplant is by intraperitoneal injection of 0.1 ml. of dilute ascitic fluid containing 10^6 cell of lymphocytic leukemia P388. The test compounds are administered intraperitoneally on days one, 5 and 9 (relative to tumor inoculation) at various doses. The animals are weighed and survivors are recorded on a regular basis for 30 days. The median survival time and the ratio of survival time for treated (T)/control (C) animals are calculated. The positive control compound is 5-fluorouracil given as a 60-mg./kg. injection. The results of this test with representative compounds of the present invention appear in Table I. The criterion for efficacy is $T/C \times 100 \geq 125\%$.

TABLE I

Lymphocytic Leukemia P388 Test			
Compound	Dose mg./kg.	Median Survival Time (Days)	T/C \times 100 (Percent)
Leuco-1,4-bis[(2-dimethylamino-ethyl)amino]-5,8-dihydroxy-anthraquinone	100	24.5	245
	50	24.5	245
	25	19.0	190
	12	17.5	175
	6	16.0	160
	3	14.5	145
	1.5	13.0	130
Control	0	10.0	—
5-Fluorouracil	60	19.0	190
1,4-Bis[(2-dimethylaminoethyl)-amino]-5,8-dihydroxy-anthraquinone	50	25.0	278
	25	20.5	228
	12	23.0	256
	6	21.0	233
	3	19.5	217
Control	0	9.0	—
5-Fluorouracil	60	19.5	217
Leuco-1,4-bis(2-morpholinoethyl-amino)-5,8-dihydroxy-anthraquinone	200	13.0	137
	100	12.0	126
	50	11.0	116
	25	12.0	126
Control	0	9.5	—
5-Fluorouracil	60	19.5	205
1,4-Bis(2-morpholinoethylamino)-5,8-dihydroxy-anthraquinone	200	14.0	147
	100	12.0	126
	50	11.0	116
Control	0	9.5	—
5-Fluorouracil	60	19.5	205

TABLE I-continued

Lymphocytic Leukemia P388 Test			
Compound	Dose mg./kg.	Median Survival Time (Days)	T/C x 100 (Percent)
Leuco-1,4-bis(2-diethylamino-ethylamino)-5,8-dihydroxy-anthraquinone	200	17.0	179
	100	17.0	179
	50	15.0	158
	25	13.0	137
	12	12.0	126
Control	0	9.5	—
5-Fluorouracil	60	19.5	205
1,4-Bis(2-diethylaminoethylamino)-5,8-dihydroxy-anthraquinone	200	20.0	210
	100	18.0	189
	50	15.0	158
	25	16.0	168
	12	12.0	126
Control	0	9.5	—
5-Fluorouracil	60	19.5	205
Leuco-1,4-bis[2-(1-pyrrolidinyl)-ethylamino]-5,8-dihydroxy-anthraquinone	200	23.0	209
	100	19.0	173
	50	16.0	145
	25	15.0	136
Control	0	11.0	—
5-Fluorouracil	60	20.0	182
1,4-Bis[2-(1-pyrrolidinyl)ethylamino]-5,8-dihydroxy-anthraquinone	100	24.0	218
	50	23.0	209
	25	21.0	191
	12	18.0	164
Control	0	11.0	—
5-Fluorouracil	60	20.0	182
1,4-Bis(3-dimethylaminopropylamino)-5,8-dihydroxy-anthraquinone	50	15.5	129
	25	15.5	129
	12	15.0	125
Control	0	12.0	—
5-Fluorouracil	60	19.5	162
Leuco-1,4-bis(2-aminoethylamino)-5,8-dihydroxy-anthraquinone	100	19.0	158
	50	23.0	192
	25	19.0	158
	12	18.0	150
Control	0	12.0	—
6-Fluorouracil	60	19.5	162
Leuco-1,4-bis(3-aminopropylamino)-5,8-dihydroxy-anthraquinone	200	18.0	150
	100	18.0	150
	50	16.0	133
	25	18.0	150
	12	16.0	133
Control	0	12.0	—
5-Fluorouracil	60	19.5	162
Leuco-1,4-bis[2-(2-methylaminoethylamino)ethylamino]-5,8-dihydroxyanthraquinone	200	2.0	18.0
	100	26.0	236.0
	50	28.0	255.0
	1	21.0	191.0
	12.5	16.0	145.0
	6.2	15.0	136
Control	0	11.0	—
5-Fluorouracil	60	17.0	170
Leuco-1,4-bis[2-dimethylaminopropylamino]-5,8-dihydroxyanthraquinone	200	18.0	200
	100	15.0	167
	50	14.0	156
	25	13.0	144
	12.5	11.0	122
Control	0	9.0	—
5-Fluorouracil	60	18.5	206
1,4-Bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone Dihydrochloride	12.5	13.0	130
	6.2	20.0	200
	3.1	22.0	220
	1.5	> 29.0	> 290
	0.78	> 29.0	> 290
	0.39	27.0	270
	0.19	25.0	250
	0.09	21.0	210
	0.04	20.0	200
Control	0	10.0	—
5-Fluorouracil	60	20.0	200
1,4-Bis[2-(1-piperazinyl)ethylamino]-5,8-dihydroxyanthraquinone	200	7.0	78
	100	21.0	233
	50	16.0	178
	25	15.0	167
	12.5	14.0	156
Control	0	9.0	—
5-Fluorouracil	60	18.5	206
1,4-Bis[2-(methylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydro-	25	9.0	86
	12.5	16.0	152

TABLE I-continued

Lymphocytic Leukemia P388 Test			
Compound	Dose mg./kg.	Median Survival Time (Days)	T/C × 100 (Percent)
chloride	6.2	20.0	190
	3.1	22.0	210
	1.5	22.5	214
	0.78	18.5	176
	0.39	19.5	186
	0.19	18.5	176
	0.09	18.0	171
	0.04	17.0	162
Control	0	10.5	—
5-Fluorouracil	60	13.0	171
Leuco-1,4-bis[2-(2-hydroxyethylamino)	25	12.0	114
ethylamino]-5,8-dihydroxyanthraquinone	12.5	23.5	224
	6.2	23.0	219
	3.1	26.0	248
	1.5	>30.0	>286
	0.78	28.0	267
	0.39	22.0	209
	0.19	21.5	205
	0.09	21.5	205
	0.04	18.5	176
Control	0	10.5	—
5-Fluorouracil	60	18.0	171
Leuco-1,4-bis(4-aminobutyl-	400	20.0	190
amino)-5,8-dihydroxyanthra-	300	18.0	171
quinone	200	17.0	162
	100	14.0	133
Control	0	10.5	—
5-Fluorouracil	60	17.5	162
Leuco-1,4-bis[2-(methyl-	50	6.0	55
amino)ethylamino]-5,8-	25	19.0	173
dihydroxyanthraquinone	12.5	19.0	173
	6.2	21.0	191
	3.1	15.0	136
	1.5	13.0	118
Control	0	11.0	—
5-Fluorouracil	60	18.5	168
Leuco-1,4-bis[2-(2-isopropyl-	100	8.0	73
amino)ethylamino]-5,8-dihy-	50	19.0	173
droxyanthraquinone	25	17.0	155
	12.5	15.0	136
Control	0	11.0	—
5-Fluorouracil	60	20.5	186
1,4-Bis[2-(2-aminoethylamino)	200	17.0	162
ethylamino]-5,8-dihydroxyanth-	100	16.0	152
raquinone	50	14.0	133
	25	13.0	124
Control	0	10.5	—
5-Fluorouracil	60	17.0	162
Leuco-1,4-[2-(di(β-hydroxy-	200	19.0	190
ethyl)amino]ethylamino-5,8-	100	17.0	170
dihydroxyanthraquinone	50	16.0	160
	25	15.0	150
	12.5	13.5	135
	6.2	12.0	120
Control	0	10.0	—
5-Fluorouracil	40	18.0	180
5,8-Bis[2-(2-hydroxy-1-pro-	25	12.0	120
pylanino)ethylamino]1,4-di-	12.5	24.0	240
hydroxyanthraquinone dihy-	6.2	23.0	230
drochloride	3.1	22.0	220
	1.56	19.0	190
	0.78	19.0	190
	0.39	17.5	175
Control	0	10.0	—
5-Fluorouracil	40	18.0	180
1,4-Bis[2,2-(1-morpholino)ethyl-	200	9.5	95
amino]ethylamino]5,8-dihydroxyan-	100	20.0	200
thraquinone tetrahydrochloride	50	18.5	185
	25	19.5	195
	12.5	15.0	150
	6.2	14.0	140
	3.1	12.0	120
Control	0	10.0	—
5-Fluorouracil	40	18.0	180
1,4-Bis[2-(3-hydroxy-1-propyl-	25	8.5	77
amino)ethylamino]5,8-dihydroxy-	12.5	>30.0	>273
anthraquinone dihydrochloride	6.25	26.0	236
	3.1	25.0	227
	1.56	22.0	200

TABLE I-continued

Lymphocytic Leukemia P388 Test			
Compound	Dose mg./kg.	Median Survival Time (Days)	T/C x 100 (Percent)
Control	0.78	21.5	195
5-Fluorouracil	0	11.0	—
Leuco-1,4-bis[2-(3-hydroxy-1-propylamino)ethylamino]5,8-dihydroxyanthraquinone	40	18.0	164
	200	14.0	127
	100	38.0	345
	50	34.0	309
	25	22.0	200
	12.5	19.5	177
	6.25	16.5	150
	3.1	18.5	168
	1.56	19.5	177
	0.78	18.0	164
Control	0	11.0	—
5-Fluorouracil	40	17.0	155
1,4-Bis[2-(di(β-hydroxyethyl)amino)ethylamino]5,8-dihydroxyanthraquinone dihydrochloride	200	> 30.0	> 333
	100	22.0	244
	50	20.5	228
	25	21.5	239
	12.5	18.5	206
	6.2	18.5	206
	3.1	19.0	211
	1.56	16.0	178
	0.78	14.5	161
Control	0	9.0	—
5-Fluorouracil	60	20.5	228
Leuco-1,4-bis[3-(2-hydroxyethylamino)-1-propylamino]5,8-dihydroxyanthraquinone	200	33.5	305
	100	27.5	250
	50	25.0	227
	25	18.5	168
	12.5	19.0	173
	6.25	18.0	164
	3.12	15.0	136
Control	0	11.0	—
5-Fluorouracil	40	17.5	159
Leuco-1,4-bis[2-(2-hydroxy-1-propylamino)ethylamino]5,8-dihydroxyanthraquinone	200	9.0	82
	100	26.5	241
	50	24.0	218
	25	20.5	186
	12.5	21.5	195
	6.25	20.0	182
Control	0	11.0	—
5-Fluorouracil	40	17.5	159
1,4-Bis[3-(2-hydroxyethylamino)-1-propylamino]5,8-dihydroxyanthraquinone dihydrochloride	100	12.5	114
	50	32.0	291
	25	26.5	241
	12.5	22.5	205
	6.25	19.0	173
	3.12	19.0	173
	1.56	16.0	145
	0.78	15.0	136
Control	0	11.0	—
5-Fluorouracil	40	17.5	159
1,4-Bis[2-(1-aziridino)ethylamino]-5,8-dihydroxyanthraquinone	100	28.5	285
	50	21.5	215
	25	20.0	200
	12.5	20.5	205
	6.25	18.5	185
	3.12	19.5	195
	1.56	17.0	170
	0.78	14.0	140
Control	0	11.0	—
5-Fluorouracil	60	20.5	205
1,4-Bis[2-(2-methylaminoethylamino)ethylamino]-5,8-dihydroxyanthraquinone tetrahydrochloride	100	22.0	220
	50	22.0	220
	25	19.5	195
	12.5	17.0	170
	6.25	16.0	160
	1.12	13.5	135
	1.56	13.0	130
Control	0	10.0	—
5-Fluorouracil	40	16.0	160
1,4-Bis[2-aminoethylamino]-5,8-dihydroxyanthraquinone dihydrochloride	12.5	8.0	73
	6.2	15.5	141
	3.1	30.0	273
	1.56	20.0	182
	0.78	24.5	223
	0.39	25.5	232
	0.19	23.0	209
Control	0	11.0	—

TABLE I-continued

Lymphocytic Leukemia P388 Test			
Compound	Dose mg./kg.	Median Survival Time (Days)	T/C \times 100 (Percent)
5-Fluorouracil	60	20.5	186

Lymphocytic leukemia P388 test

The procedure used is the same as for the previously 10 described test for lymphocytic leukemia P388 except that the test compounds are administered orally at various doses rather than intraperitoneally. The results of this test with typical compounds of the present invention appear in Table II. The criterion for efficacy is 15 $T/C \times 100 \geq 125\%$.

TABLE II

Lymphocytic Leukemia P388 Test (Oral Drug Administration)			
Compound	Dose mg./kg.	Median Survival Time (Days)	T/C \times 100 (Percent)
Leuco-1,4-bis[(2-dimethylamino-ethyl)amino]-5,8-dihydroxy-anthraquinone	50	16.0	160
	25	13.5	135
	12	12.5	125
Control	0	10.0	—
5-Fluorouracil*	60	19.0	190
1,4-Bis[(2-dimethylaminoethyl)-amino]-5,8-dihydroxy-anthraquinone	12	16.0	139
	6	16.0	139
	3	15.0	130
Control	0	11.5	—
5-Fluorouracil*	60	20.0	174

*5-Fluorouracil administered intraperitoneally.

Melanotic Melanoma B16

The animals used are C57BC/6 mice, all of the same sex, weighing a minimum of 17 g. and all within a 3-g. 35 weight range. There are normally 10 animals per test group. A one-gram portion of melanotic melanoma B16

tumor is homogenized in 10 ml. of cold balanced salt solution and a 0.5-ml. aliquot of the homogenate is im-
 10 planted intraperitoneally into each of the test mice. The test compounds are administered intraperitoneally on days one through 9 (relative to tumor inoculation) at various doses. The animals are weighed and survivors are recorded on a regular basis for 60 days. The median
 15 survival time and the ratio of survival time for treated (T)/control (C) animals are calculated. The positive

control compound is 5-fluorouracil given as a 20-
 mg./kg. injection. The results of this test with represen-
 tative compounds of the present invention appear in
 35 Table III. The criterion for efficacy is $T/C \times 100 \geq 125\%$.

TABLE III

Melanotic Melanoma B16 Test			
Compound	Dose mg./kg.	Median Survival Time (Days)	T/C \times 100 (Percent)
Leuco-1,4-bis[(2-dimethylamino-ethyl)amino]-5,8-dihydroxy-anthraquinone	25	25.0	151
	12	23.0	139
	6	21.5	130
	3	21.0	127
Control	0	16.5	—
5-Fluorouracil	20	25.0	151
1,4-Bis[(2-dimethylaminoethyl)-amino]-5,8-dihydroxy-anthraquinone	25	24.5	136
	12	28.5	158
	6	27.0	150
	3	25.5	142
Control	0	18.0	—
5-Fluorouracil	20	26.0	144
Leuco-1,4-bis[(2-diethylamino-ethyl)amino]-5,8-dihydroxy-anthraquinone	50	23.0	139
Control	0	16.5	—
5-Fluorouracil	20	25.0	151
1,4-Bis[(2-diethylaminoethyl)-amino]-5,8-dihydroxy-anthraquinone	50	20.5	125
Control	0	16.5	—
5-Fluorouracil	20	25.0	151
Leuco-1,4-bis[[2-(1-pyrrolidinyl)-ethyl]amino]-5,8-dihydroxy-anthraquinone	50	23.0	144
	25	22.0	137
	12	21.0	131
Control	0	16.0	—
5-Fluorouracil	20	26.5	166
1,4-Bis[[2-(1-pyrrolidinyl)ethyl]-amino]-5,8-dihydroxy-anthraquinone	25	24.5	153
	12	22.0	137
	6	22.0	137
Control	0	16.0	—
5-Fluorouracil	20	26.5	166
1,4-Bis[(3-dimethylaminopropyl)-amino]-5,8-dihydroxy-anthraquinone	25	20.0	125

TABLE III-continued

Melanotic Melanoma B16 Test			
Compound	Dose mg./kg.	Median Survival Time (Days)	T/C × 100 (Percent)
Control	0	16.0	—
5-Fluorouracil	20	26.5	166
Leuco-1,4-bis[(2-aminoethyl)- amino]-5,8-dihydroxy-anthraquinone	12	32.0	200
Control	0	16.0	—
5-Fluorouracil	20	26.5	166
Leuco-1,4-bis(3-aminopropylamino)- 5,8-dihydroxy-anthraquinone	50	31.5	197
	25	27.0	169
	12	23.5	147
	6	22.5	141
Control	0	16.0	—
5-Fluorouracil	20	26.5	166
Leuco-1,4-bis[2-(2-methylamino- ethylamino)-5,8-dihydroxyanthra- quinone	50	12.5	73
	25	35.0	206
	12.5	39.5	232
	6.2	28.5	168
Control	0	17.0	—
5-Fluorouracil	20	30.0	176
1,4-Bis[2-(1-piperaziny)- ethylamino]-5,8-dihydroxyanthra- quinone	50	34.5	203
	25	30.5	179
	12.5	26.0	153
	6	22.0	129
	3	20.5	121
Control	0	17.0	—
5-Fluorouracil	20.0	30	176
1,4-Bis[2-(2-aminoethylamino) ethylamino]-5,8-dihydroxyanthra- quinone	50	24.0	150
	25	22.5	141
	12	22.0	138
	6	20.0	125
Control	0	16.0	—
5-Fluorouracil	20	27.0	169
Leuco-1,4-bis[2-dimethylamino- propylamino]-5,8-dihydroxyanthra- quinone	100	21.0	124
	50	28.5	168
	25	24.5	144
	12.5	20.5	121
	6	19.5	115
Control	0	17.0	—
5-Fluorouracil	20	30.0	176
1,4-Bis[2-(2-hydroxyethylamino) ethylamino]-5,8-dihydroxyanthra- quinone dihydrochloride	12	11.0	73
	6	15.0	100
	3	>28.5	>190
	1.5	>34.0	>227
	0.7	>34.0	>227
	0.3	34.0	227
Control	0	15.0	—
5-Fluorouracil	60	23.0	153
Leuco-1,4-bis[2-(2-isopropylamino) ethylamino]-5,8-dihydroxyanthra- quinone	50	6.5	39
	25	31.0	188
	12	30.0	182
	6	25.0	151
Control	0	16.5	—
5-Fluorouracil	20	16.5	100
1,4-Bis[2-(methylamino)ethyl- amino]-5,8-dihydroxyanthra- quinone dihydrochloride	12.5	11.5	59
	6.2	26.5	136
	3.1	49.0	251
	1.5	33.0	169
	0.78	35.0	179
	0.39	25.0	128
	0.19	29.5	151
Control	0	19.5	—
5-Fluorouracil	60	25.0	128
Leuco-1,4-bis(4-aminobutyl- amino)-5,8-dihydroxyanthra- quinone	100	21.0	124
	50	20.0	118
	25	18.5	109
	12	16.0	94
Control	0	17.0	—
5-Fluorouracil	20	30.0	176
Leuco-1,4-bis[2-(2-hydroxy- ethylamino(ethylamino)-5,8- dihydroxyanthraquinone	6	9.5	59
	3	20.5	128
	1.5	30.0	187
	0.75	28.5	178
	0.37	22.0	137
Control	0	16.0	—
5-Fluorouracil	20	27.5	172
Leuco-1,4-bis[2-(methylamino) ethylamino]-5,8-dihydroxyanthra- quinone	12	28.0	175
	6	32.5	203
	3	31.0	194
	1.5	36.0	225
	0.7	27.5	172

TABLE III-continued

Compound	Melanotic Melanoma B16 Test		
	Dose mg./kg.	Median Survival Time (Days)	T/C × 100 (Percent)
Control	0	16.0	—
5-Fluorouracil	20	27.5	172

Ridgway Osteogenic Sarcoma

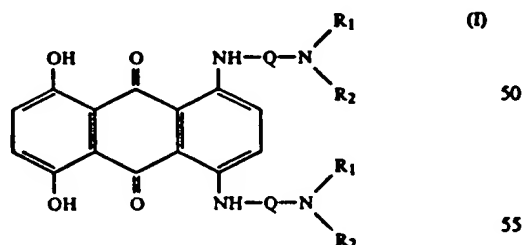
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The animals used are AKD₂F₁/J mice, all of the same sex, weighing a minimum of 17 g. and all within a three-gram weight range. There are normally 8 animals per test group. The tumor is administered subcutaneously by trocar as five 2-mm. fragments per mouse. The test compounds are administered intraperitoneally every 4 days for a total of 6 inoculations beginning on day 15 (relative to tumor inoculation) at various doses. The animals are weighed and survivors are recorded on a regular basis for 90 days. The regression of tumors is recorded in all test animals. Table IV gives the result of this test with a representative compound of this invention in terms of the percentage of animals showing tumor regression.

TABLE IV

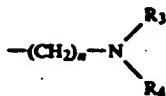
Compound	Ridgway Osteogenic Sarcoma								
	1 Day Before			7 Days After Therapy Stopped				63 Days After	
	Dose (mg./kg.)	No. Mice Per Group	Tumor (mm.) ²	No. Without Tumors/No. Survivors	Tumor (mm.) ²	% Inhibition Tumor Growth	% Showing 50% Tumor Regression	Median Survival (Days)	T/C (Percent)
Placebo	—	8	64	0/5	1189		0	44.5	
1,4-Bis[(2-di- methylamino- ethyl)amino]-	100	7	77	2/5	52	96	28	48	108
5,8-dihydroxy- anthraquinone	50	8	68	2/6	263	78	25	92.5	208
Methotrexate	25	8	82	0/8	653	41	0	78	175
	12	7	84	0/3	470	61	0	37	83
	6	7	83	0/6	960	19	0	57.5	129
	25	8	51	1/6	546	54	12	52.5	118
	12	8	52	0/9	916	23	0	49	110
	6	8	54	0/4	758	36	0	46	103
Vincristine	1.5	8	42	4/4	0	100	100	68	153
	1.0	6	99	6/6	0	100	100	85	191
	0.5	7	94	4/7	77	93	57	83	186

A preferred embodiment of the present invention may be represented by the following general formula: 45



wherein Q is as hereinbefore defined; R₁ is hydrogen, alkyl having from 1 to 4 carbon atoms or monohydroxyalkyl having from 2 to 4 carbon atoms and wherein the carbon atom alpha to the nitrogen atom may not bear an hydroxy group; R₂ is monohydroxyalkyl having from 2 to 4 carbon atoms and wherein the carbon atom alpha to the nitrogen atom may not bear an hydroxy group, dihydroxyalkyl having from 3 to 6 carbon atoms and wherein the carbon atom alpha to the nitrogen atom may not bear an hydroxy group or a moiety of the formula: 60

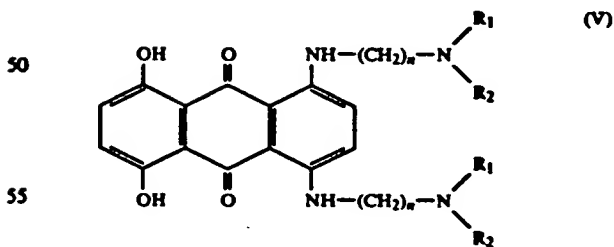
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15 wherein n , R_3 and R_4 are as hereinbefore defined; with the proviso that the ratio of the total number of carbon atoms to the sum of the total number of oxygen atoms plus the total number of nitrogen atoms in each of the side chains at the 1-position and the 4-position may not
 20 exceed four. The preferred embodiment includes the corresponding leuco bases of the aromatic bases (I), the tautomers thereof, and the non-toxic pharmaceutically acceptable acid-addition salts thereof.

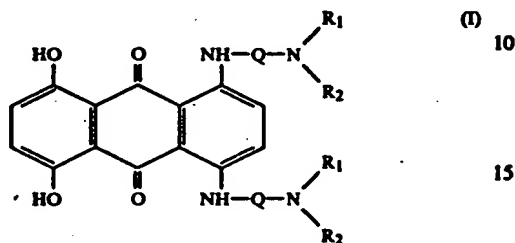
Another preferred embodiment of the present inven-

45 tion may be represented by the following general formula:



60 wherein n is an integer from 2 to 4, inclusive, and R_1 and R_2 are as defined for the preceding preferred embodiment with the proviso that the ratio of the total number of carbon atoms to the sum of total number of oxygen atoms plus the total number of nitrogen atoms in each of the side chains at the 1-position and the 4-position may
 65 not exceed four. This preferred embodiment also includes the corresponding leuco bases of the aromatic bases (V), the tautomers thereof, and the non-toxic pharmaceutically acceptable acid-addition salts thereof.

Also embraced within the purview of the present invention are therapeutic compositions of matter useful for ameliorating cancer diseases in mammals and containing certain 5,8-dihydroxy-1,4-bis(substituted-amino)anthraquinones (or the leuco bases and non-toxic acid-addition salts thereof) which may be represented by the following structural formula:



wherein R_1 is hydrogen or alkyl having from 1 to 4 carbon atoms, R_2 is hydrogen or alkyl having from 1 to 4 carbon atoms, R_1 and R_2 taken together with their associated N(itrogen) is as hereinbefore defined for R_3 and R_4 taken together with their associated N(itrogen), and Q is as hereinbefore defined.

The active ingredients of the therapeutic compositions and the novel compounds of the present invention inhibit transplanted mouse tumor growth when administered in amounts ranging from about 5 mg. to about 200 mg. per kilogram of body weight per day. A preferred dosage regimen for optimum results would be from about 5 mg. to about 50 mg. per kilogram of body weight per day, and such dosage units are employed that a total of from about 350 mg. to about 3.5 grams of the active compound for a subject of about 70 kg. of body weight are administered in a 24-hour period. This dosage regimen may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decided practical advantage is that the active compound may be administered in any convenient manner such as by the oral, intravenous, intramuscular, or subcutaneous routes.

The active compounds may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and 200 milligrams of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a

lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparations and formulations.

The active compounds may also be administered parenterally or intraperitoneally. Solutions of the active compound as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the

active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically-acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 0.1 to about 400 mg., with from about one to about 30 mg. being preferred. Expressed in proportions, the active compound is generally present in from about 0.1 to about 400 mg./ml. of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

This invention will be described in greater detail in conjunction with the following specific examples.

EXAMPLE 1

Leuco-1,4-bis[(2-dimethylaminoethyl)amino]-5,8-dihydroxy-anthraquinone

A reaction mixture comprising 10.58 g. of N,N-dimethylethylenediamine, 60 ml. of N,N,N',N'-tetramethylethylenediamine and 10.96 g. of leuco-1,4,5,8-tetrahydroxyanthraquinone is flushed with nitrogen and stirred under nitrogen for 2 hours while heating with an oil bath kept at 49°-51° C. The mixture is allowed to cool under nitrogen. The solid is collected and washed with ethanol giving 14.78 g. of the desired product as a dark red-brown solid.

EXAMPLE 2

1,4-Bis[(2-dimethylaminoethyl)amino]-5,8-dihydroxyanthraquinone

A 12.00-g. portion of leuco-1,4-bis[(2-dimethylaminoethyl)amino]-5,8-dihydroxy-anthraquinone in 100 ml. of nitrobenzene is heated under reflux for 15 minutes and then filtered while hot. The filtrate is reheated to boiling, allowed to cool, and the solid is collected and

washed with ethanol giving 8.44 g. of the desired product as blue-black crystals, mp. 236°–238° C.

EXAMPLE 3

5 Leuco-1,4-bis(2-morpholinoethylamino)-5,8-dihydroxyanthraquinone

A solution of 15.62 g. of N-(2-aminoethyl)morpholine in 40 ml. of N,N,N',N'-tetramethylethylenediamine is de-aerated by bubbling nitrogen through it for 15 min-
10 utes. A 10.97-g. portion of leuco-1,4,5,8-tetrahydroxyanthraquinone is added slowly with stirring and the suspension is treated as described in Example 1, giving 18.07 g. of the desired product as an olive solid, mpm
15 223°–227° C.

EXAMPLE 4

1,4-Bis(2-morpholinoethylamino)-5,8-dihydroxyanthraquinone

20 A 13.90-g. portion of leuco-1,4-bis(2-morpholinoethylamino)-5,8-dihydroxyanthraquinone in 100 ml. of nitrobenzene is oxidized as described in Example 2 giving 10.30 g. of the desired product as black rods, mp. 241°–243° C.
25

EXAMPLE 5

Leuco-1,4-bis[(2-diethylaminoethyl)amino]-5,8-dihydroxyanthraquinone

30 The procedure of Example 3 is repeated using 13.95 g. of N,N-diethylethylenediamine in place of the N-(2-aminoethyl)morpholine, giving 13.97 g. of the desired product as a red-brown solid, mp. 182°–185° C.

EXAMPLE 6

35 1,4-Bis[(2-diethylaminoethyl)amino]-5,8-dihydroxyanthraquinone

A 10.90-g. portion of leuco-1,4-bis[(2-diethylaminoethyl)amino]-5,8-dihydroxyanthraquinone is oxidized as
40 described in Example 2 giving 6.35 g. of the desired product as blue-black needles, mp. 202°–204° C.

EXAMPLE 7

45 Leuco-1,4-bis[2-(1-pyrrolidinyl)ethylamino]-5,8-dihydroxyanthraquinone

The procedure of Example 3 is repeated using 12.05 g. of N-2-pyrrolidinoethylamine, in place of the N-(2-aminoethyl)morpholine, and 80 ml. of N,N,N',N'-tetramethylethylenediamine, giving 13.24 g. of the desired
50 product as a red-brown solid, mp. 180°–185° C.

EXAMPLE 8

55 1,4-Bis[2-(1-pyrrolidinyl)ethylamino]-5,8-dihydroxyanthraquinone

An 8.61-g. portion of leuco-1,4-bis[(2-(1-pyrrolidinyl)ethyl)amino]-5,8-dihydroxyanthraquinone is oxidized as described in Example 2. The reaction mixture is evaporated to dryness and the residue recrystallized
60 from toluene, giving 5.12 g. of the desired product as blue-black crystals, mp. 193°–196° C.

EXAMPLE 9

65 Leuco-1,4-bis[2-(methylamino)ethylamino]-5,8-dihydroxyanthraquinone

The procedure of Example 7 is repeated using 8.90 g. of N-methylethylenediamine in place of the N-2-pyr-

rolidinoethylamine, giving 13.73-g. of the desired product as a dark green solid, mp. 157°-160° C.

EXAMPLE 10

Leuco-1,4-bis[(3-dimethylaminopropyl)amino]-5,8-dihydroxyanthraquinone 5

Nitrogen is bubbled through an 80-ml. portion of dimethylaminopropylamine for 15 minutes. A 10.97-g. portion of leuco-1,4,5,8-tetrahydroanthraquinone is added slowly with stirring. The mixture is heated under nitrogen at 50°-52° C. for 2 hours and then allowed to cool. The solid is collected and washed with cold ethanol giving 5.59-g. of dark, orange-red crystals, mp. 115°-118° C. 10 15

EXAMPLE 11

1,4-Bis[(3-dimethylaminopropyl)amino]-5,8-dihydroxyanthraquinone

A suspension of 6.00-g. of leuco-1,4-bis[(3-dimethylaminopropyl)amino]-5,8-dihydroxyanthraquinone in 60 ml. of N,N,N',N'-tetramethylethylenediamine is heated on a steam bath under reflux while air is bubbled in for 12 hours. The solution is cooled, producing a solid which is collected and washed twice with heptane and once with petroleum ether. This solid is recrystallized by extracting with 350 ml. of hot heptane, filtering and concentrating to 300 ml. Crystallization and washing with petroleum ether gives 3.72 g. of the desired product as black needles, mp. 154°-157° C. 20 25 30

EXAMPLE 12

Leuco-1,4-bis(2-aminoethylamino)-5,8-dihydroxyanthraquinone

A reaction mixture comprising 10.97-g. of leuco-1,4,5,8-tetrahydroxyanthraquinone in 80 ml. of de-aerated N,N,N',N'-tetramethylethylenediamine containing 7.22 g. of ethylenediamine is heated and stirred under nitrogen at 48°-50° C. for one hour. The mixture is allowed to stand under a slow flow of nitrogen, producing a solid which is collected and washed with ethyl acetate, acetonitrile and petroleum ether giving 13.8 g. of the desired product as a red-black solid. 35 40

EXAMPLE 13

Leuco-1,4-bis(3-aminopropylamino)-5,8-dihydroxyanthraquinone 45

A suspension of 10.97 g. of leuco-1,4,5,8-tetrahydroxyanthraquinone in a de-aerated solution of 8.90 g. of 1,3-diaminopropane in 80 ml. of N,N,N',N'-tetramethylethylenediamine is stirred and heated at 49° C. for one hour under nitrogen, then allowed to cool. The resulting solid is collected and washed with cold ethanol giving 14.21 g. of the desired product as a black solid. 50 55

EXAMPLE 14

Leuco-1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone 60

A suspension of 12.5 g. of 2-(2-aminoethylamino)ethanol in 40 ml. of N,N,N',N'-tetramethylethylenediamine is stirred and de-aerated by bubbling nitrogen in for 15 minutes. A 10.97-g. portion of leuco-1,4,5,8-tetrahydroxyanthraquinone is gradually added with stirring. The suspension is heated and stirred under nitrogen in an oil bath at 50°-52° C. for 5 hours. The mixture is allowed to stand and cool under nitrogen for 12 65

hours. The solid is collected by decantation, macerated in ethanol, collected and washed with ethanol giving 15.06 g. of the desired product as a green-gray solid, mp. 129°-131° C.

EXAMPLE 15

Leuco-1,4-bis[2-[di(β -hydroxyethyl)amino]ethylamino]-5,8-dihydroxyanthraquinone

A solution of 17.8 g. of N,N-di(2-hydroxyethyl)ethylenediamine in 100 ml. of methanol is cooled with an ice bath, stirred, and de-aerated by bubbling in nitrogen for 15 minutes. A 10.97-gram portion of leuco-1,4,5,8-tetrahydroxyanthraquinone is gradually added with stirring and continued cooling. The suspension is heated and stirred under nitrogen in an oil bath at 50°-52° C. for one hour and the mixture is then allowed to stand and cool under nitrogen overnight. The solid is collected and washed with ethanol giving 14.8 g. of a red-brown solid, m.p. 165°-168° C.

EXAMPLE 16

1,4-Bis[2-(methylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride

To a suspension of 11.60 g. (0.03 mole) of leuco-1,4-bis[2-(methylamino)ethylamino]-5,8-dihydroxyanthraquinone in 200 ml. of 2-methoxyethanol was added gradually with stirring 15 ml. of 8 N ethanolic hydrogen chloride. The system was chilled with an ice bath and stirred as 7.50 g. (0.0305 mole) of chloranil powder was gradually added. The mixture was stirred overnight at room temperature and diluted with 600 ml. of ether. The solid was collected and washed with tetrahydrofuran. The product (14.16 g.) was recrystallized by dissolving it in 130 ml. of water and adding 650 ml. of acetone to give 13.15 g. of a blue-black solid.

EXAMPLE 17

1,4-Bis[2-(2-aminoethylamino)ethylamino]-5,8-dihydroxyanthraquinone

Following the general procedure of Example 3, a mixture of 10.97-g. of leuco-1,4,5,8-tetrahydroxyanthraquinone, 80 ml. of N,N,N',N'-tetramethylethylenediamine and 21.84-g. (0.24 mole) of diethylenetriamine soon gave a thick, congealed mass which prevented effective stirring so the reaction time was extended to 24 hours. The mixture was allowed to cool and the supernatant liquid was decanted and discarded. A solution of the congealed mass in 100 ml. of methanol was filtered, then allowed to oxidize in the air for four days in a partially covered flask. The gelatinous mass which had separated became solid when the oxidation mixture was agitated with 200 ml. of acetonitrile and then allowed to stand for one hour. After the solid was collected and washed first with acetonitrile, then with ether, it amounted to 10.88 g. of a blue-black powder.

EXAMPLE 18

Leuco-1,4-bis(4-aminobutylamino)-5,8-dihydroxyanthraquinone

Following the general procedure of Example 3 but using 45 ml. of 1,4-diaminobutane as the primary amine component, there was obtained 12.20 g. of product as a dull grey-green solid.

EXAMPLE 19

Leuco-1,4-bis[2-dimethylaminopropylamino]-5,8-dihydroxyanthraquinone

The reaction of 12.26 g. of 2-dimethylaminopropylamine with 10.97 g. of leuco-1,4,5,8-tetrahydroxyanthraquinone in 100 ml. of ethanol for one hour by the procedure of Example 1 gives 7.29 g. of red-brown crystals.

EXAMPLE 20

Leuco-1,4-bis[2-(2-methylaminoethylamino)ethylamino]-5,8-dihydroxyanthraquinone

To a solution of 14.10 g. of 1-methyl diethylenetriamine in 50 ml. of ethanol and 40 ml. of N,N,N',N'-tetramethylethylenediamine is added 10.97 g. of leuco-1,4,5,8-tetrahydroxyanthraquinone as in Example 1. The mixture is heated at 50° and stirred under nitrogen for one hour, chilled with an ice bath, the solid collected and washed with cold ethanol to give 7.23 g. of green-black crystals, m.p. 108°-111° C.

EXAMPLE 21

Leuco-1,4-bis[2-(2-dimethylaminoethylamino)ethylamino]-5,8-dihydroxyanthraquinone

The reaction of N-(dimethylaminoethyl)ethylenediamine with leuco-1,4,5,8-tetrahydroxyanthraquinone by the procedure of Example 20 gives the title compound.

EXAMPLE 22

Leuco-1,4-bis[2-(1-piperazinyl)ethylamino]-5,8-dihydroxyanthraquinone

The procedure of Example 20 applied to 15.50 g. of N-(2-aminoethyl)piperazine gives 3.92 g. of a black powder which does not melt by 350° C. and is discarded. The mother liquor and ethanol washes, on standing and partly evaporating during two weeks in an unstoppered flask, deposit a solid which is collected and washed with ethanol to give 6.19 g. of the title compound as a black solid, m.p. 200°-203° C.

EXAMPLE 23

1,4-Bis(2-aminoethylamino)-5,8-dihydroxyanthraquinone dihydrochloride

Oxidation with chloranil of 28.25 g. of the product of Example 12 by the procedure of Example 16 gives 29.66 g. of a crude, blue-black solid which is then extracted by stirring for 14 hours with 800 ml. of water. Solids are removed by centrifugation and the supernatant solution freeze-dried, leaving 16.38 g. of a blue-black solid which is unmelted by 350° C.

EXAMPLE 24

1,4-Bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone Dihydrochloride

Chloranil oxidation of 17.86 g. of the product of Example 14 by the procedure of Example 16 gives (without recrystallization) 21.34 g. of blue-black solid, m.p. 203°-205° C.

EXAMPLE 25

1,4-Bis[2-(2-methylaminoethylamino)ethylamino]-5,8-dihydroxyanthraquinone Tetrahydrochloride

The product of Example 20 (11.70 g.) is oxidized with chloranil by the procedure of Example 16, giving 18.03 g. of blue-black solid, m.p. 190°-203° C.

EXAMPLE 26

1,4-Bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone

In a modification of the synthesis of Example 14 the solvent used is 100 ml. of ethanol. The mother liquor from the leuco product is allowed to stand for two weeks in an unstoppered flask, whereupon the oxidized product separates. It is collected and washed with ethanol, then recrystallized from ethanol, giving blue-black crystals, m.p. 175°-177° C.

EXAMPLE 27

Leuco-1,4-bis[3-(2-hydroxyethylamino)-1-propylamino]-5,8-dihydroxyanthraquinone

The procedure of Example 15 is used with a solution of 14.18 g. of 2-(3-aminopropylamino)ethanol in 100 ml. of ethanol. The resulting solution is filtered and the filtrate diluted with 300 ml. of ether, precipitating the product as a goo. After decantation of the supernatant solution the goo is caused to crystallize by agitating it with 100 ml. of tetrahydrofuran. Washing with ethanol gives 12.56 g. of green-black solid, m.p. 101°-104° C.

EXAMPLE 28

1,4-Bis[3-(2-hydroxyethylamino)-1-propylamino]-5,8-dihydroxyanthraquinone dihydrochloride

Oxidation of 9.95 g. of leuco-1,4-bis[3-(2-hydroxyethylamino)propylamino]-5,8-dihydroxyanthraquinone with chloranil as in Example 16 gives 11.70 g. of a blue solid which does not melt by 350° C.

EXAMPLE 29

Leuco-1,4-bis[2-(3-hydroxy-1-propylamino)ethylamino]-5,8-dihydroxyanthraquinone

The procedure of Example 15 is paralleled with 14.18 g. of N-(3-hydroxypropyl)ethylenediamine in 100 ml. of ethanol to give 14.63 g. of red-brown crystals, m.p. 58°-60° C.

EXAMPLE 30

1,4-Bis[2-(3-hydroxy-1-propylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride

Chloranil oxidation of 10.77 g. of the product of Example 29 by the procedure of Example 16 yielded 11.64 g. of a dark blue solid, m.p. 210°-216° C.

EXAMPLE 31

Leuco-1,4-bis[2-(2-hydroxy-1-propylamino)ethylamino]-5,8-dihydroxyanthraquinone

With 14.18 g. of 1-(2-aminoethylamino)-2-propanol in 100 ml. of ethanol the procedure of Example 15 yields 17.61 g. of green-black crystals, m.p. 50°-60° C.

EXAMPLE 32

1,4-Bis[2-(2-hydroxy-1-propylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride

A filtered solution of 14.44 g. of leuco-1,4-bis[2-(2-hydroxy-1-propylamino)ethylamino]-1,4-dihydroxyanthraquinone in 215 ml. of 2-methoxyethanol is oxidized with 7.65 g. of chloranil by the procedure of Example 16, affording 16.75 g. of purple solid, m.p. 177°-185° C.

EXAMPLE 33

Leuco-1,4-bis[2-(2-(2-hydroxyethylamino)ethylamino)ethylamino]-5,8-dihydroxyanthraquinone

The procedure of example 15 used with a solution of 17.67 g. of 2-[2-(2-aminoethylamino)ethylamino]ethanol in 100 ml. of methanol gives a solution which is filtered, then diluted with 300 ml. of ether, precipitating a goo which hardens on standing overnight. Hardening is completed by thorough maceration of the solid in the solvent. The solid is collected and washed with ether, yielding 16.82 g. of a green-black solid. This solid remains granular if stored at -25° C., but coalesces into a solid cake if stored at 25° C.

EXAMPLE 34

1,4-Bis[2-(2-(2-hydroxyethylamino)ethylamino)ethylamino]-5,8-dihydroxyanthraquinone tetrahydrochloride

Chloranil oxidation of 12.10 g. of the product of Example 33 by the method of Example 16, including three additional washings of the solid with methanol, gives 12.46 g. of dark blue, solid product.

EXAMPLE 35

1,4-Bis[2-(2,3-dihydroxypropylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride

By the procedure of Example 15 a solution of 16.10 g. of 3-(2-aminoethylamino)-1,2-propanediol [A. R. Surrey, C. M. Suter and J. S. Buck, J. Am. Chem. Soc., 74, 4102(1952)] in 100 ml. of methanol gives a goo which is separated from solvent by chilling with an ice bath, then decanting. The goo is washed four times by stirring 1.5 hours at 25° with 100-ml. portions of methanol, chilling with an ice bath, then decanting. A filtered solution of the goo in 280 ml. of 2-methoxyethanol is oxidized with 10.01 g. of chloranil by the method of Example 16. The product is additionally washed with ethanol, giving 15.25 g. of a blue-black solid, m.p. 191°-193° C.

EXAMPLE 36

Leuco-1,4-bis[2-(1-aziridino)ethylamino]-5,8-dihydroxyanthraquinone

With 10.33 g. of N-(2-aminoethyl)aziridine in 80 ml. of N,N,N',N'-tetramethylethylenediamine the procedure of Example 15 gives a stiff gum. The next day the supernatant solution is discarded, 100 ml. of ether is added and the gum periodically macerated therein for another day, when the gum is mostly hardened. Hardening is completed by maceration during three washings of the solid with ether, giving 17.66 g. of blue-black, granular powder.

EXAMPLE 37

1,4-Bis[2-(1-aziridino)ethylamino]-5,8-dihydroxyanthraquinone

5 To a suspension of 4.10 g. of the product of Example 36 in 40 ml. of chloroform is added a solution of 1.74 g. of diethyl azodicarboxylate in 25 ml. of chloroform. The mixture is stirred for 20 minutes, the resulting dark blue solution is filtered, and the filtrate is evaporated at
 10 $\leq 30^\circ$. A solution of the residue in 40 ml. of chloroform is stirred five minutes with 2 g. of decolorizing carbon, filtered and washed through with another 25 ml. of chloroform. Addition of 100 ml. of ether to the filtrates precipitates a gum which is eliminated by decantation-
 15 filtration. The filtrates deposit crystals which are washed sparingly with acetone. The chloroform-ether mother liquor, chilled at -60° C., deposits a second crop of crystals which is washed with ether and with methanol. A solution of both crops of crystals in 20 ml.
 20 of chloroform is stirred with decolorizing carbon, filtered, evaporated at $\leq 25^\circ$ C. to a volume of 5 ml., diluted with 20 ml. of ether, then chilled at -60° C. The resulting blue-black crystals, washed with ether, amount to 0.64 g., m.p. 168° - 170° C. In thin-layer chromatography on silica gel the product is moved as a blue
 25 spot by chloroform-triethylamine-methanol, 27/3/1 (ratios by volume).

EXAMPLE 38

1,4-Bis[2-[2-(1-morpholino)ethylamino]ethylamino]-5,8-dihydroxyanthraquinone tetrahydrochloride

A solution of 20.80 g. of N-(morpholinoethyl)ethylenediamine in 100 ml. of ethanol is used in the procedure of Example 15 to give a solution which is filtered
 35 and diluted with 900 ml. of ether, precipitating a goo. The supernatant solution is decanted, the goo dissolved in 175 ml. of 2-methoxyethanol and oxidized with 5.29 g. of chloranil by the method of Example 16, giving 17.7
 40 g. of dark blue solid.

EXAMPLE 39

Leuco-1,4-Bis[2-(acetamido)ethylamino]-5,8-dihydroxyanthraquinone

45 A solution of 12.26 g. of N-acetylene diamine in 100 ml. of ethanol in the procedure of Example 15 gives 15.27 g. of dark, red-brown solid, m.p. 125° C.

EXAMPLE 40

1,4-Bis[2-(acetamido)ethylamino]-5,8-dihydroxyanthraquinone

A suspension of 11.95 g. of leuco-1,4-bis[2-(acetamido)ethylamino]-5,8-dihydroxyanthraquinone is
 55 oxidized with 6.76 g. of chloranil during 61 hours by the method of Example 16, giving a very acidic hydrochloride salt which is converted to the free base by four washings with water. Crystallization from 110 ml. of dimethyl sulfoxide (boiling only 2 minutes and not attempting a hot filtration), then washing with dimethyl
 60 sulfoxide and with ethanol gives 7.76 g. of blue-black solid, m.p. 273° - 274° C.

EXAMPLE 41

1,4-Bis[2-[N-(2-hydroxyethyl)trifluoroacetamido]ethylamino]-5,8-dihydroxyanthraquinone

A suspension of 1.50 g. of 1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone in

75 ml. of ethyl trifluoroacetate and 75 ml. of methanol is stirred for 10 minutes. Evaporation of the resulting solution in vacuo at 30° C. leaves a residue which is washed and macerated with methylene chloride, giving 2.11 g. of blue-black solid, m.p. 162° C.

EXAMPLE 42

1,4-Bis[2-amino-2-carboxyethylamino]-5,8-dihydroxyanthraquinone. $\frac{1}{2}$ HCl

To a solution of 6.23 g. of dl- α,β -diaminopropionic acid in 30 ml. of warm water is added 1.078 g. of lithium hydroxide and 60 ml. of dimethyl sulfoxide. The system is flushed with nitrogen and 4.12 g. of leuco-1,4,5,8-tetrahydroxyanthraquinone is added gradually with stirring. The mixture is stirred and heated with an oil bath at 50°, first for 15 hours under nitrogen, then for 21 hours as the initial product is oxidized by bubbling in a stream of air. Thin-layer chromatography on silica gel with methanol-water-concentrated ammonia (25/5/1 by volume) shows all the product spots to be blue when the oxidation is complete. After the mixture is cool the solids are removed by filtration and washed once with dimethyl sulfoxide-water (2/1). Addition of 400 ml. of methanol to the filtrates precipitates a solid which is collected and washed with methanol. Further washing with a total of 13. ml. of 0.01 N aqueous acetic acid dissolves virtually all of the solid. Addition of 3 ml. of concentrated hydrochloric acid to the acetic acid filtrates precipitates a blue-black solid which is washed with acetone to give 0.24 g. of the product.

EXAMPLE 43

Leuco-1,4-bis[2-(2-methoxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone

An ethanol solution of N-(2-methoxyethyl)ethylenediamine (U.S. Pat. No. 3,454,640) reacts in the procedure of Example 15 to give the title compound.

EXAMPLE 44

1,4-Bis[2(1,3-oxazolidin-1-yl)ethylamino]-5,8-dihydroxyanthraquinone

A solution of 1.62 g. of 37% aqueous formaldehyde solution in 50 ml. of water is stirred overnight with 4.44 g. of 1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone. The resulting solid is washed with water to give the product.

EXAMPLE 45

1,4-Bis[2-(tetrahydro-1,3-oxazin-1-yl)ethylamino]-5,8-dihydroxyanthraquinone

A solution of 1.62 ml. of 37% aqueous formaldehyde in 50 ml. of 0.4 N aqueous sodium hydroxide is stirred overnight with 5.45 g. of 1,4-bis[2-(3-hydroxy-1-propylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride. The product is obtained by washing the resulting solid with water.

EXAMPLE 46

1,4-Bis[2-(1,3-oxazolidin-2-one-1-yl)ethylamino]-5,8-dihydroxyanthraquinone

A solution of 0.020 g. of sodium in 25 ml. of methanol is stirred and heated under reflux overnight with 75 ml. of diethyl carbonate and 4.44 g. of 1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone. The mixture is allowed to cool. It is stirred with

0.1 ml. of acetic acid, the solid is collected by filtration and washed with methanol to give the product.

EXAMPLE 47

5 1,4-Bis[2-(1,3-oxazin-2-one-1-yl)ethylamino]-5,8-dihydroxyanthraquinone

A solution of 0.48 g. of sodium in 25 ml. of methanol is stirred and heated overnight with 75 ml. of diethyl carbonate and 5.45 g. of 1,4-bis[2-(3-hydroxy-1-propylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride. After the mixture cools it is stirred with 0.1 ml. of acetic acid. The solid product is collected by filtration and washed with methanol and then with water.

EXAMPLE 48

20 1,4-Bis[2-{di(β -hydroxyethyl)amino}ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride

Chloranil oxidation of 10.77 g. of the product of Example 15 by the method of Example 16 gives 11.64 g. of a dark blue solid, m.p. 216° C.

EXAMPLE 49

25 Preparation of 50 mg. Tablets

	Per Tablet	Per 10,000 Tablets
30	0.050 gm. 1,4-bis(3-aminopropylamino)-5,8-dihydroxyanthraquinone	500 gm.
	0.080 gm. Lactose	800 gm.
	0.010 gm. Corn Starch (for mix)	100 gm.
	0.008 gm. Corn Starch (for paste)	75 gm.
	0.148 gm.	1475 gm.
35	0.002 gm. Magnesium stearate (1%)	15 gm.
	0.150 gm.	1490 gm.

The 1,4-bis(3-aminopropylamino)-5,8-dihydroxyanthraquinone, lactose and corn starch (for mix) are blended together. The corn starch (for paste) is suspended in 600 ml. of water and heated with stirring to form a paste. This paste is then used to granulate the mixed powders. Additional water is used if necessary. The wet granules are passed through a No. 8 hand screen and dried at 120° F. The dry granules are then passed through a No. 16 screen. The mixture is lubricated with 1% magnesium stearate and compressed into tablets in a suitable tableting machine.

EXAMPLE 50

50 Preparation of Oral Suspension

	Ingredient	Amount
55	Leuco-1,4-bis(3-aminopropylamino)-5,8-dihydroxyanthraquinone	300 mg.
	Sorbitol solution (70% N.F.)	40 ml.
	Sodium benzoate	150 mg.
	Saccharin	10 mg.
	Red dye	50 mg.
60	Cherry flavor	50 ml.
	Distilled water qs. ad.	100 ml.

The sorbitol solution is added to 40 ml. of distilled water and the leuco-1,4-bis(3-aminopropylamino)-5,8-dihydroxyanthraquinone is suspended therein. The saccharin, sodium benzoate, flavor and dye are added and dissolved. The volume is adjusted to 100 ml. with distilled water. Each ml. of syrup contains 5 mg. of leuco-

1,4-bis(3-aminopropylamino)-5,8-dihydroxyanthraquinone.

EXAMPLE 51

Preparation of Parenteral Solution

In a solution of 700 ml. of propylene glycol and 200 ml. of water for injection is suspended 20.0 grams of 1,4-bis[3-(dimethylamino)propylamino]-5,8-dihydroxyanthraquinone dihydrochloride with stirring. After suspension is complete, the pH is adjusted to 5.5 with hydrochloric acid and the volume is made up to 1000 ml. with water for injection. The formulation is sterilized, filled into 5.0 ml. ampoules each containing 2.0 ml. (representing 40 mg. of drug) and sealed under nitrogen.

EXAMPLE 52

1,4-Bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone disuccinate salt

A mixture of 222 mg. of 1,4-bis[2-(2-hydroxyethylamino)-ethylamino]-5,8-dihydroxyanthraquinone, 118 mg. of succinic acid, and 50 ml. of ethanol is heated under reflux for 30 minutes to give the title compound.

EXAMPLE 53

1,4-Bis[2-(3-hydroxypropylamino)ethylamino]-5,8-dihydroxyanthraquinone dimalate salt

A mixture of 228 mg. of 1,4-bis[2-(3-hydroxypropylamino)-ethylamino]-5,8-dihydroxyanthraquinone, 134 mg. of DL-malic acid, and 50 ml. of ethanol is heated under reflux for 30 minutes to give the title compound.

EXAMPLE 54

1,4-Bis[2-(2-hydroxypropylamino)ethylamino]-5,8-dihydroxyanthraquinone dilactate salt

A mixture of 228 mg. of 1,4-bis[2-(2-hydroxypropylamino)-ethylamino]-5,8-dihydroxyanthraquinone, 120 mg. of 80% DL-lactic acid, and 10 ml. of ethanol is heated on a steam bath for 10 minutes, cooled, treated with 50 ml. of acetone and cooled to obtain the title compound.

EXAMPLE 55

Preparation of 50 mg. Tablets

Per Tablet		Per 10,000 Tablets	
0.050 gm.	1,4-Bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride	500 gm.	50
0.080 gm.	Lactose	800 gm.	
0.010 gm.	Corn Starch (for mix)	100 gm.	
0.008 gm.	Corn Starch (for paste)	75 gm.	
0.148 gm.		1475 gm.	55
0.002 gm.	Magnesium Stearate (1%)	15 gm.	
0.150 gm.		1490 gm.	

The 1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride, lactose and corn starch (for mix) are blended together. The corn starch (for paste) is suspended in 600 ml. of water and heated with stirring to form a paste. This paste is then used to granulate the mixed powders. Additional water is used if necessary. The wet granules are passed through a No. 8 hand screen and dried at 120° F. The dry granules are then passed through a No. 16 screen. The mixture is lubricated with 1% magnesium stearate

and compressed into tablets in a suitable tableting machine.

EXAMPLE 56

Preparation of Oral Suspension

	Ingredient	Amount
10	1,4-Bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride	500 mg.
	Sorbitol solution (70% N.F.)	40 ml.
	Sodium benzoate	150 mg.
	Saccharin	10 mg.
	Red dye	50 mg.
	Cherry flavor	50 ml.
15	Distilled water qs ad	100 ml.

The sorbitol solution is added to 40 ml. of distilled water and the 1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride is suspended therein. The saccharin, sodium benzoate, flavor and dye are added and dissolved. The volume is adjusted to 100 ml. with distilled water. Each ml. of syrup contains 5 mg. of 1,4-bis[2-(2-hydroxyethylamino)ethylamino]-5,8-dihydroxyanthraquinone dihydrochloride.

EXAMPLE 57

1,4-Bis[2-(3-hydroxypropylamino)ethylamino]-5,8-dihydroxyanthraquinone diacetate salt

A mixture of 228 mg. of 1,4-bis[2-(3-hydroxypropylamino)ethylamino]-5,8-dihydroxyanthraquinone, 60 mg. of glacial acetic acid, and 50 ml. of ethanol is heated under reflux for 30 minutes to give the title compound.

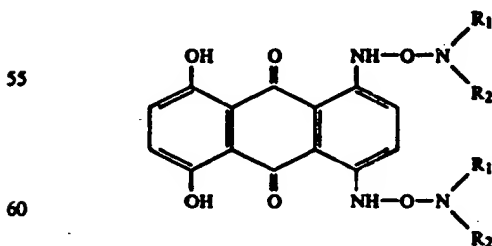
EXAMPLE 58

1,4-Bis[2-(2-hydroxypropylamino)ethylamino]-5,8-dihydroxyanthraquinone diacetate salt

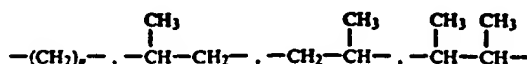
A mixture of 228 mg. of 1,4-bis[2-(2-hydroxypropylamino)ethylamino]-5,8-dihydroxyanthraquinone, 60 mg. of glacial acetic acid, and 10 ml. of ethanol is heated on a steam bath for 10 minutes, cooled, treated with 50 ml. of acetone and cooled to obtain the title compound.

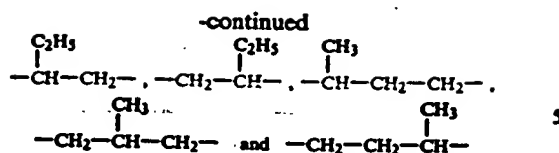
We claim:

1. A pharmaceutical composition in dosage unit form comprising from about one to about 30 mg. of a compound selected from the group consisting of those of the formula:



wherein Q is a divalent moiety selected from the group consisting of those of the formulae:





wherein n is an integer from 2 to 4, inclusive; R₁ and R₂ are each individually selected from the group consisting of hydrogen, alkyl having from 1 to 4 carbon atoms and monohydroxyalkyl having from 2 to 4 carbon atoms and wherein the carbon atom alpha to the nitrogen atom may not bear an hydroxy group with the proviso that R₁ and R₂ may not both be hydrogen or alkyl; and the pharmacologically acceptable acid-addition salts thereof; in association with a pharmaceutical carrier.

2. A composition according to claim 1 wherein the compound is a salt of sulfuric acid.

3. A composition according to claim 1 wherein the compound is a salt of hydrochloric acid.

4. A composition according to claim 1 wherein the compound is a salt of sulfamic acid.

5. A composition according to claim 1 wherein the compound is a salt of citric acid.

6. A composition according to claim 1 wherein the compound is a salt of lactic acid.

7. A composition according to claim 1 wherein the compound is a salt of succinic acid.

8. A composition according to claim 1 wherein the compound is a salt of acetic acid.

9. A composition according to claim 1 wherein the compound is a salt of gluconic acid.

10. The composition according to claim 1 wherein Q is ethylene and R₁ and R₂ are both β -hydroxyethyl and in the aromatic free base form.

11. The composition according to claim 1 wherein Q is ethylene, R₁ is hydrogen, and R₂ is β -hydroxyethyl and in the disuccinate salt form.

12. The composition according to claim 1 wherein Q is ethylene, R₁ is hydrogen, and R₂ is β -hydroxyethyl and in the dihydrochloride salt form.

13. The composition according to claim 1 wherein Q is ethylene, R₁ is hydrogen, and R₂ is 3-hydroxypropyl and in the dihydrobromide salt form.

14. The composition according to claim 1 wherein Q is ethylene, R₁ is hydrogen, and R₂ is 2-hydroxypropyl and in the disuccinate salt form.

15. The composition according to claim 1 wherein Q is trimethylene, R₁ is hydrogen, and R₂ is β -hydroxyethyl and in the diacetate salt form.

16. The composition according to claim 1 wherein Q is $-\text{CH}_2\text{CH}(\text{CH}_3)-$, R₁ is hydrogen, and R₂ is β -hydroxyethyl and in the dimalate salt form.

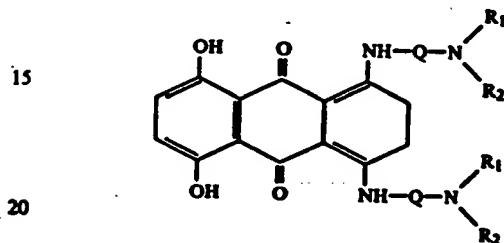
17. The composition according to claim 1 wherein Q is ethylene, R₁ is hydrogen, and R₂ is β -hydroxyethyl and in the aromatic free base form.

18. A composition according to claim 17 in its pharmacologically acceptable acid-addition salt form.

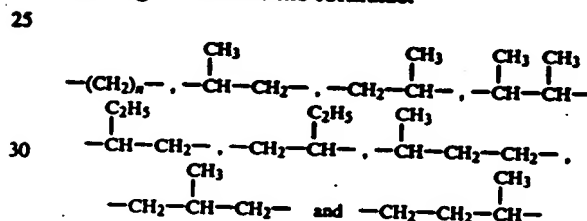
19. The composition according to claim 1 wherein Q is ethylene, R₁ is hydrogen, and R₂ is β -hydroxyethyl and in the digluconate salt form.

20. The composition according to claim 1 wherein Q is ethylene, R₁ is hydrogen, and R₂ is β -hydroxyethyl and in the dibenzoate salt form.

21. A pharmaceutical composition in dosage unit form comprising from about one to about 30 mg. of a compound selected from the group consisting of those of the formula:



wherein Q is a divalent moiety selected from the group consisting of those of the formulae:



wherein n is an integer from 2 to 4, inclusive; R₁ and R₂ are each individually selected from the group consisting of hydrogen, alkyl having from 1 to 4 carbon atoms and monohydroxyalkyl having from 2 to 4 carbon atoms and wherein the carbon atom alpha to the nitrogen atom may not bear an hydroxy group with the proviso that R₁ and R₂ may not both be hydrogen or alkyl; and the pharmacologically acceptable acid-addition salts thereof; in association with a pharmaceutical carrier.

22. A composition according to claim 21 wherein the compound is a salt of phosphoric acid.

23. A composition according to claim 21 wherein the compound is a salt of hydrobromic acid.

24. A composition according to claim 21 wherein the compound is a salt of malic acid.

25. A composition according to claim 21 wherein the compound is a salt of tartaric acid.

26. A composition according to claim 21 wherein the compound is a salt of benzoic acid.

27. A composition according to claim 21 wherein the compound is a salt of ascorbic acid.

28. The composition according to claim 21 wherein Q is ethylene, R₁ is hydrogen, and R₂ is β -hydroxyethyl and in the leuco free base form.

29. The composition according to claim 21 wherein Q is ethylene, R₁ is hydrogen, and R₂ is 2-hydroxypropyl and in the leuco free base form.

• • • • •

EXHIBIT B

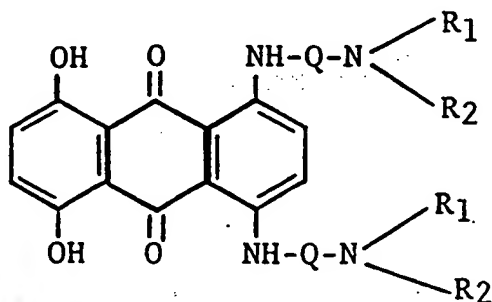
UNITED STATES PATENT OFFICE CERTIFICATE OF CORRECTION

Patent No. 4,278,689 Dated July 14, 1981

Inventor(s) KEITH CHADWICK MURDOCK and FREDERICK EMIL DURR

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

IN THE CLAIMS: Claim 1, Column 30, Lines 52-60



Signed and Sealed this

Twenty-second Day of September 1981



Attest:

Ruth M. Wray

Attesting Officer

Gerald J. Mossinghoff

GERALD J. MOSSINGHOFF

Commissioner of Patents and Trademarks

EXHIBIT C

This brief description of the activities undertaken by the assignee of record of U.S. Patent No. 4278689 during the regulatory review period with respect to the approved product consists of two attachments. The first is a 109 page computer printout covering the period of IND No. 16-332 while the second is a 19 page computer printout covering the period of NDA No. 19-297. These two computer printouts list all submissions to, responses from, and transactions with the Food and Drug Administration during the regulatory review period.

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

L Apr-12-79

79-1

DRS

110128

SUBMITTED INDIA FOR CL 232,315. ATTACHED: PART X INCLUDES CLINICAL TRIAL PLAN FOR PHASE I AND EARLY PHASE II & PROTOCOL FOR INITIAL PHASE I STUDY TO BE CONDUCTED BY J. DURANT; PART IX INCLUDES CVS FOR DRS. DURANT, GAMS, AND MURRAY. QUALIFICATIONS & PROTOCOLS FOR EACH ADDITIONAL INVEST. WILL BE FILED BEFORE STUDY BEGINS.

F May-21-79

DRS

110127

ACKNOWLEDGE RECEIPT OF INDIA PURSUANT TO SECTION 505(i) AND ASSIGNMENT OF INDIA NO. 16-332 FOR CL 232,315.

L Jun-01-79

79-2

DRS

110125

STUDY PROPOSED FOR DR. ARNOLD CANCELLED (ADMINISTR. REASONS) & INITIAL STUDY TO BE PERFORMED BY DR. D. VON HOFF. ITEMS SUBMITTED: V REVISED QC MONOGRAPH OF CL 232,315 PARENTERAL; IX CHECKLIST & CVS FOR VON HOFF & DR. COLTMAN; X REVISED CLINICAL TRIAL PLAN & PROTOCOL FOR VON HOFF'S STUDY.

F Aug-06-79

DRS

110154

REF. SUBJECT INDIA, RECOMMENDATIONS & REQUESTS: MEDICAL: APPLY RADIONUCLIDE TEST FOR CARDIAC TOX. IN UNIV. OF TEXAS STUDY TO REPLACE CANCELLED STUDY AT UNIV. OF ALABAMA. CHEMISTRY: 19 REQUESTS ON SPECS. AFFECTING CONTROLS & MANUFACTURING. PHARMACOLOGY: REQUEST ANIMAL MODELS DEMONSTRATING COMPARATIVE CARDIOTOX. OF SUBJECT DRUG AND DOXORUBICIN ETC., ANALAGOUS TO A CLINICAL SITUATION.

F Sep-17-79

DRS

110129

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

re. IND AND AMDT. OF 6/1/79. RECOMMENDATION:
RADIONUCLIDE TECH. FOR CARDIAC TOX. PROPOSED IN
CANCELLED PHASE I STUDY AT UNIV. OF ALABAMA SHOULD
BE APPLIED TO INITIAL PHASE I STUDY AT UNIV. OF
TEXAS.

L Sep-19-79

79-3

DRS

110130

RESP TO FDA LETTER (8/6/79) AND SUPPLYING
QUALIFICATIONS FOR NEW INVEST & PROTOCOL FOR HIS
STUDY. ITEMS ATTACHED: AMEND. A, RESPONSE TO CHEM.
ITEMS 1-9 (IN 8/6 LETT.); PART VI, RESPONSE TO
PHARMACOLOGY REQUEST (IN 8/6 LETT.); PART IX,
CHECKLIST & CVs FOR ALBERTS & HERMAN; PART X,
RESPONSE FOR MURRAY TO MEDICAL RECOMMEND. (IN 8/6
LETT.); PROTO. FOR ALBERTS STUDY TO INCORPORATE
CARDIAC TOX BY RADIONUCLIDE TECH.

L Nov-26-79

79-4

DRS

110131

AMENDED IND: PART IX, CHECKLIST & CVs FOR
ADDITIONAL INVEST. A. LIPTON & ASSOCIATE DR.
HARVEY; PART X, PROTOCOL FOR LIPTON STUDY -
APPROVED BY CLINICAL INVEST. COMMITTEE. STUDY BY
D. ALBERTS SUSPENDED AT REQUEST OF DR. JOHNSON
(10/15). AFTER DISCUSSED SUPPORTING DATA, JOHNSON
AGREED TO RESUMPTION OF STUDY. E. MCKEON OF LED.
INFORMED AND STUDY NOW IN PROGRESS.

L Dec-04-79

79-5

DRS

110132

re. FDA LETTER 8/6/79 CHEMISTRY (ITEM 1); REQUEST
RELEASE SPECIFICATIONS ON RAW MATERIALS AS
SUPPLIED BY MANUFACT. AND ANY ADDIT. CONTROLS
PERFORMED BY LED. ATTACH. A, (LED. LETTER
9/19/79), INDICATED INFO. TO BE FURNISHED A.S.A.P
(INCLUDED PART V). ITEMS SUBMITTED: PART V,
AVAILABLE MANUFACT. RELEASE SPECS.; PART X,
ADDENDA TO PROTOCOL SUBMITTED 11/2/79 FOR A.
LIPTON STUDY.

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

F Dec-14-79				DRS	110133
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REF. INDA AND AMEND. OF 9/19 AND 11/2 AND TELE. CONVERSATION 10/15/79 BETWEEN (LED) MURRAY AND (AGENCY) JOHNSON AND 10/31/79 CONVERSATION BETWEEN (UNIV. ARIZONA) ALBERTS AND JOHNSON. AGREED 10/31, NO OBJECTION TO ALBERTS CONTINUING PHASE I STUDY PROVIDED CLOSE CONTACT WITH VON HOFF IS KEPT REGARDING DEVELOPMENTS IN HIS RELATED STUDY.

L Mar-04-80			80-1	DRS	110134
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AMENDED INDA: PART IX, CHECKLIST AND CVs FOR J. HOLCENBERG AND T. VIETTI, AND DRs. FUSNER, LAND & BHANOT; PART X, PROTOCOL FOR HOLLENBERG STUDY, PROTOCOL FOR VIETTI STUDY, & ADDENDA TO PROTOCOL SUBMIT. 9/19/79 FOR ALBERTS STUDY.

L Apr-30-80			80-2	DRS	110135
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AMENDED INDA: PART IX, CHECKLIST OF CURRENTLY ACTIVE INVESTIGATORS; PART X, ANNUAL PROGRESS REPORT.

L Jun-20-80			80-3	DRS	110136
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AMENDED INDA: PART IX, CVs DRs. WYNERT AND SIMMONDS, ASSOCIATES WITH LIPTON AND STUDY FILED 10/4/79; PART X, CLINICAL REPORT FOR VON HOFF STUDY.

L Aug-19-80			80-4	DRS	110137
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AMENDED. INDA PROVIDE FOR PHASE II STUDIES. CLINICAL TRIAL PLAN DESCRIBES ARRANGE. WITH NCI FOR ONCOLOGY GROUP STUDIES. ITEMS INCLUDED: PART VI, ADDITIONAL PRECLINICAL STUDIES; PART VII, UPDATED INVEST BROCHURE; PART IX, UPDATED CV FOR VON HOFF (ORIGINALLY LISTED AS AN INVEST 6/1/79); PART X, CLINICAL TRIAL PLAN, 7 PROTOCOLS FOR PHASE II STUDIES, CLINICAL REPORT FOR ALBERTS STUDY.

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTHONE	CL 232,315	ANTICANCER AGENT	

L Oct-08-80			80-5	DRS	110138
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AMENDED INDIA: PART I, USAN NOMENCLATURE STATEMENT;
PART X, ADDENDUM TO PROTOCOL SUBMIT. 11/2/79 FOR
LIPTON STUDY (EARLIER ADDENDA FILED 12/4/79).
ALSO, TAYLOR PHARMACAL CO., ILL. CONTRACTED TO
MANUFACT. & PACKAGE CL 232,315 FOR LED. EXHIBIT I,
MANUFACT. & CONTROL DOCUMENT. & GMP STATEMENT.
BOTTLES & FINISHED STOCK TO LED. FOR QC RELEASE
TEST PRIOR TO CLINICAL TRIAL.

L Oct-22-80			80-6	DRS	110139
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AMENDED INDIA: PART IX, CVs DRs. BERGAMINI AND
SEDLIS TO ASSIST T. VIETTI; PART X, AMEND. TO
PROTOCOL SUBMIT. 3/4/80 FOR HOLCENBERG STUDY.

L Nov-13-80			80-7	DRS	110140
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AMENDED INDIA: PART IX, UPDATED CV FOR D. ALBERTS &
CVs FOR DRs. WOOLFENDA, PATTON AND AAPRO TO ASSIST
ALBERTS; PART X, PROTOCOL FOR ALBERTS NEW STUDY.
PROTOCOL AMEND. FILED 10/22/80 FOR HOLCENBERG
STUDY ALSO APPLIES TO VIETTI STUDY SUBMIT. 3/4/80.

L Nov-24-80			80-8	DRS	110141
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AMENDED INDIA: PART IX, CHECKLISTS AND CVs FOR 27
ADDITIONAL INVEST., UPDATED CV FOR VON HOFF. ALL
INVESTIGATORS WILL FOLLOW 7 PHASE II PROTOCOLS
SUBMIT. 8/19/80 AND WILL REPORT THROUGH VON HOFF.

L Dec-16-80			80-9	DRS	110142
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AMENDED INDIA: PART X, TWO ADDITIONAL PROTOCOLS FOR
PHASE II STUDIES AND REPORTED THROUGH VON HOFF.
MEMBERS OF GROUP NAMED IN SUBMISSION OF 8/19/80
AND 11/24/80.

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315	ANTICANCER AGENT		

L Feb-06-81			81-1	DRS	110143
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AMENDED INDA: PART III, FORMULAS; PART VII, LABELS; PART X, ADDITIONAL PROTOCOL FOR PHASE II STUDIES, AND REPORTED THROUGH VON HOFF. MEMBERS OF GROUP NAMED IN SUBMISSION OF 8/19/80 AND 11/24/80, AMEND. TO PROTOCOL FOR HOLCENBERH & VIETTI SUBMIT. 3/4/80 AND AMENDED 10/22/80.

L Mar-31-81			81-2	DRS	110144
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AMEND INDA: PART III, FORMULA; PART IV, SYNTHESIS RADIOLABELED MITOX.; PART VII, LABELING; PART IX, CHECKLIST SHOWING 3rd STUDY BY ALBERTS (QUALIFICATION SUBMIT 11/13/80), CHECKLISTS 21 ADDIT. INVEST & THEIR CVs, CV FOR DAVIS (ASSOCIATE ALBERTS); PART X, PROTOCOL ALBERTS NEW STUDY, 10 PROTOCOLS FOR PHASE II STUDIES, RESULTS REPORTED THROUGH GAMS, 3 PROTO. FOR PHASE II AND REPORT THROUGH VON HOFF, CLINICAL REPORT FOR LIPTON STUDY.

L Apr-10-81			81-3	DRS	110145
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AMENDED INDA: PART V, ADDIT. STABILITY DATA; PART IX, CHECKLIST FOR ADDITIONAL INVEST. J. ALLEGRA, AND REPORTED THROUGH GAMS, REVISED CHECKLIST NAMING D. WOODWARD MONITOR FOR ALBERTS STUDY SUBMITTED 3/31/81, CV FOR ALLEGRA AND WOODWARD.

L Jun-02-81			81-4	DRS	110146
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AMENDED INDA: PART IX, CHECKLIST OF CURRENT ACTIVE INVEST., CV FOR T. TERZAKIS; PART X, ANNUAL PROGRESS REPORT, AMEND. TO VON HOFF PHASE I STUDY (SUBMIT. 6/1/79), VON HOFF STUDY REPORT.

L Jun-08-81			81-5	DRS	110147
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Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

AMENDED INDAs: PART IX, CHECKLIST AND CV FOR ADDITIONAL INVEST. J. NEIHART AND CVs FOR ASSOCIATES DRs. MISER AND MALSPEIS; PART X, PROTOCOL FOR NEIDHART STUDY, AMEND. TO HOLCENBERG AND VIETTI STUDIES SUBMIT. 3/4/80 AND AMENDED 10/22/80 AND 2/6/81.

L Jul-08-81 81-6 DRS 110148

AMEND INDAs: PART VII, UPDATE BROCHURE FOR INVEST, SAMPLE LETTER WITH ATTACH FROM LEV DESCRIBING INCIDENTS OF CARDIOTOX IN PATS TREATED WITH MITOX. LETTER SENT TO ALL LED INVEST & NCI NOTIFIED BY LEV; PART IX, UPDATED CV VIETTI; PART X, AMEND TO PROTOCOL FOR HOLCENBERG & VIETTI STUDIES SUBMIT 3/4/80 & AMEND 10/22/80, 2/6 & 6/8/81, PROT FOR PHASE II STUDY BY POG, HOLCENBERG & VIETTI COMBINE CLIN REP, ADDENDUM LIPTON REP SUBMIT 3/31/81.

L Jul-31-81 81-7 DRS 110151

AMENDED INDAs: PART VI, ADDIT. PRECLINICAL STUDIES; PART VII, SAMPLE LETTER WITH ATTACH. FROM LEV SUMMARIZING 9 CASES OF CARDIOTOX. ASSOCIATED WITH MITOX. & LISTING NEW ENROLL. RESTRICTIONS - SENT TO ALL LED. INVEST.; PART IX, CVs FOR DRs. BERGAMINI, DISTELHORST, LAND, & SEDLIS (ASSOC. TERESA); PART X, REPORT OF AN ADVERSE EXPERIENCE (ONE DESCRIBED IN LEV'S LETTER 7/14/81).

L Sep-08-81 81-8 DRS 110149

AMENDED INDAs: PART X, PROTOCOL AMEND. TO ONGOING MITOXANTRONE STUDIES INITIATED BY NCI DUE TO REPORTS OF CARDIOTOX., REPORT OF AN ADVERSE EXPERIENCE.

L Oct-23-81 91-9 DRS 110157

AMENDED INDAs: PART X, AMEND. TO PROTOCOL SUBMIT. 3/31/81 FOR ALBERTS STUDY.

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332	IND	MITOXANTRONE	CL 232,315	ANTICANCER AGENT	
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F Oct-26-81				DRS	110152
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REF. INDA: REPORTED 20 CASES CONGESTIVE HEART FAILURES IN PAT. RECEIVING MITOX. REQUIRING A COMPREHENSIVE PLAN FOR FUTURE STUDIES. THIS SUBMISSION SHOULD ACT AS INTERIM PROGRESS REPORT TO INCLUDE TOTAL NO. PAT. ENTERED TO DATE, TUMOR RESPONSE & TYPE OF DOSE SCHED., LIST ALL STUDIES & WHICH STILL OPEN, & INFO. ON TOX. i.e. MOST FREQUENTLY SEEN AND PERCENT OF PAT. OCCUR. REQUEST ALSO BEING MADE OF NCI.

L Nov-30-81			81-10	DRS	110153
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RESPONSE TO FDA CORRES. 10/26/81 REGARDING EFFICACY AND SAFETY OF MITOX. ATTACHED REPORT ID'S SOURCES OF DATA AND NO. PATS. INVOLVED. MORE DETAILED REPORT TO BE SUPPLIED BY JANUARY. DRS. ALBERTS AND NEIDHART STUDIES ARE CURRENTLY ACTIVE.

L Dec-30-81			81-11	DRS	110150
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AMENDED INDA: PART V, OC MONOGRAPH & RELATED ANALYT. RESEARCH METHOD REPORT 78, UPDATE HPLC ASSAY BULK DRUG SUBSTANCE & PARENT. PREPS.; PART IX, CV & CHECKLIST FOR D. McDONALD, CV FOR R. FOWLER (ASSIST. McDONALD); PART X, PROTOCOL FOR 2 STUDIES BY McDONALD, PROTOCOL FOR PHASE II-III STUDY CONDUCTED BY SWOG & REPORTED THROUGH VON HOFF, AMEND TO PREVIOUS SUBMIT. SWOG PROTOCOLS.

L Mar-04-82			82-1	DRS	110155
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AMENDED INDA: PART IX, CHECKLIST AND CV FOR ADDITIONAL INVEST. J. STURGEON; PART X, PROTOCOL AND CRF FOR STURGEON STUDY, REPORT OF ADVERSE EXPERIENCE IN NCI-SPONSORED STUDY.

L Mar-17-82			82-2	DRS	110156
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Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315	ANTICANCER AGENT		

AMENDED INDIA: PART IX, CV M. FUJIMORI TO MONITOR STUDIES PREVIOUSLY ASSIGNED TO MURRAY OR TERZAKIS. WOODWARD & FOWLER CONTINUE TO MONITOR STUDIES INDICATED ON CHECKLIST AT TIME OF PROTOCOL FILING.

L Mar-26-82 82-3 DRS 110158

REF. FDA CORRES. 10/26/81 AND LED. RESPONSE 11/30/81. REPORT SUMMARIZ. SAFETY & EFFICACY DATA FOR MITOX. SUBMITTED. ITEMS ATTACHED: PART X, MITOX. REPORT, PROPOSED CLIN. OPERATING PLAN, DRUG EXPERIENCE REP. FROM ALBERTS CARDIAC FUNCT. STUDY (LED. SPONSOR), DRUG EXPERIENCE REP. FROM PAT. IN NCI-SPONSORED STUDIES. REQUEST FOR MEETING TO DISCUSS FUTURE CLIN. STUDIES WITH MITOX.

L Apr-20-82 82-4 DRS 110159

AMENDED INDIA: PART VI, ADDITIONAL PRECLINICAL STUDIES; PART X, FD FORM 1639 FILED 3/4/82 FOR PAT. B.B., #54585. DISCUSSION OF CARDIAC DIFFICULTIES AND "NOT CONTRIBUTING TO DEATH". AFTER FURTHER REVIEW, RELATIONSHIP WOULD BE CLASSIFIED AS "POSSIBLE". (SEE LETTER FOR MORE DETAILED DESCRIPTION OF CARDIAC DIFFICULTIES.)

L May-06-82 82-5 DRS 110126

AMENDED IND SUBMIT.: IX, CHECKLIST OF CURRENTLY ACTIVE INVEST.; X, ANNUAL PROGRESS REPORT.

L May-25-82 82-6 DRS 111759

IN ANTICIPATION OF 6/23/82 MEETING, SUBMIT 1)PROSPECTIVE CLINICAL OPERATING PLAN, 2)PROTOCOL FOR STUDY IN PATIENTS WITH BREAST CANCER.

L Jun-07-82 82-7 DRS 110351

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
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AMEND. SUBJECT INDA: PART VII, REVISED BROCHURE FOR INVEST.; PART IX, CHECKLIST STUDY BY VAP (BODEY CO-INVEST.), CVs VAP & BODEY AND ASSOC. BLUMENSCHIN, EWER, BENJAMIN, HORTOBAGYI, SCHELL, AND WALLACE; PART X, PROTOCOL FOR VAP AND BODEY STUDY.

L Jun-11-82

82-8 DRS 110515

AMEND SUBJECT INDA: PART IX, CHECKLIST & CV FOR ROWAN & ASSISTANTS TONG & BLOCK; PART X, PROTOCOL FOR CHLEBOWSKI'S STUDY.

L Jun-14-82

82-9 DRS 110514

PURSUANT TO TELE. CONVERSATION WITH JOHNSON(FDA) 6/9/82, SENDING ADDITIONAL PROTOCOLS FOR REVIEW PRIOR TO MEETING 6/23. CALL ATTENTION TO PROTOCOL SUBMIT 6/7/82 FOR VAP & BODEY STUDY (ITEM 5 ON TABLE 1 OF PROSPECTIVE CLIN. OPERATING PLAN).

L Jul-13-82

82-10 DRS 110832

AMEND SUBJECT INDA: PART VII, PHARMACY BROCHURE; PART IX, CHECKLIST & CVs FOR SILVER LEVICK GRACE ALLEGRA WOODCOCK & WOLFF, CV FOR ASSISTS PASMANTIER COLEMAN NACHMAN JAROWSKI SOLE RUGGIERO RESNICK CHIARIERI SALETAN MOLANDER(SILVER), LEVICK DESAI(LEVICK), JOHNSTON SARG(GRACE), KUBOTA RICHMAN BLUMENREICH(ALLEGRA), & GRECO HAINSWORTH BRENNER HANDE(WOLFF); PART X, PROT & CRF FOR MULTI-CENTER STUDY, DRUG EXPERT FROM NCI STUDY.

L Jul-15-82

82-11 DRS 110827

SUBMIT TO SUBJECT INDA PACKAGE 2 DRUG EXPERIENCE REPORTS FROM NCI STUDIES OMITTED FROM 7/13/82 SUBMIT.

L Jul-22-82

82-12 DRS 111760

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

AMEND SUBJECT INDIA: PART IX, CHECKLIST & CV FOR 5 NEW INVESTIGATORS & CVs FOR THEIR ASSOCIATES (REF HARD COPY LETTER FOR LIST OF NAMES); PART X, DRUG EXPERIENCE REPORT. FIVE NEW INVEST TO FOLLOW PROTOCOL SUBMIT 7/13/82.

L Jul-29-82

82-13

DRS

111062

AMEND SUBJECT INDIA: CHECKLIST & CVs FOR SPICER, PERLOFF & DUGAN, CVs FOR MITCHELL, ARDALAN, BERTRAM, GRUNBERG, KEMPF, & DANIELS (ASSIST SPICER), CVs FOR ELLISON, HYMAN, OSTER, STOOPLER, & RAPOPORT (ASSIST PERLOFF), CVs FOR SCHROEDER, BATES, & WORKMAN (ASSIST DUGAN); PART X, EXPLAIN CARDIOTOX MONITOR FOR SURGEON STUDY (SUBMIT 3/4/82). 3 INVEST ABOVE TO FOLLOW PROT SUBMIT 7/13/82.

L Aug-05-82

82-14

DRS

111092

AMEND SUBJECT INDIA: PART IX, CHECKLIST & CV FOR ROSS, CV FOR KRAMER (ASSIST ROSS). ROSS TO FOLLOW PROTOCOL SUBMIT 7/13/82.

L Aug-18-82

82-15

DRS

111185

AMEND SUBJECT INDIA: PART IX, CHECKLIST & CVs FOR MOORE, DAO & VOLBERDING, CVs FOR NEMOTO & PATEL (ASSIST DAO), CV FOR GENTILE (ASSIST ALLEGRA & WOODCOCK IN STUDY SUBMIT 7/13/82); PART X, AMEND TO PROTOCOL TO AFFECT DAO'S STUDY ONLY. ALL INVEST TO FOLLOW PROTOCOL SUBMIT 7/13/82.

L Aug-24-82

82-16

DRS

111222

AMEND SUBJECT INDIA: PART IX, CHECKLIST & UPDATED CV FOR NEIDHART & CVs FOR ASSOC BALCERZAK, BOURONCLE, DEWALD, GREVER, KRAUT, METZ, RIVEHART, ROACH, SOGONE, WALL, & WILSON; PART X, PROT FOR NEIDHART STUDY & SAMPLE COMPUTER CRF. SPONSOR FOR 1st NEIDHART STUDY (ON SINCE 11/80) TRANSFER FROM NCI TO LED. DETERMIN OF PHARMACOKINETIC PARAMETER DELETED FROM PROT OBJECTIVE. UPDATED TOX STUDIES INCLUDED.

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

L Sep-03-82			82-17	DRS	111245
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AMEND SUBJECT INDA: PART IX, CHECKLIST & CVs FOR DOTY & GOLOMB, CVs FOR KANE & REGAN (ASSIST DOTY), CVs FOR ALBAIN, BARON, GAYNOR, HOFFMAN, LARSON, NEELY, PEARSON, ULTMANN, VAN SHEPARD, & WADE (ASSIST GOLOMB). DOTY & GOLOMB TO FOLLOW PROTOCOL SUBMIT 7/13/82.

L Sep-10-82			82-18	DRS	111250
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AMEND SUBJECT INDA: PART IX, CHECKLIST FOR SILVER 2nd STUDY (QUALIF SUBMIT 7/13/82), CHECKLIST & CVs FOR ARMENTROUT, BROUN, & GOLDMAN, CVs FOR BROWER & MOORE (ASSIST SILVER), STATER (ASSIST ARMENTROUT), GALLAGHER, JOIST, D. LUEDKE, S. LUEDKE, & PETRUSKA (ASSIST BROUN), GRADY, BURNINGHAM, GALEN (ASSIST GOLDMAN); PART X, PROT TO BE FOLLOWED BY SILVER, ARMENTROUT & BROUN. GOLDMAN TO FOLLOW PROT SUBMIT 7/13/82.

L Sep-17-82			82-19	DRS	111277
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AMEND SUBJECT INDA: PART IX, CHECKLIST FOR COSTANZI 2nd STUDY, CHECKLIST & CV FOR ERSLEV, UPDATED CV FOR COSTANZI, CHECKLIST FOR BLOCK (QUALIF FILED 6/11/82), CVs FOR ALPERIN GARDNER, GUPTA, & WEISS (ASSIST COSTANZI), CVs FOR 10 ERSLEV'S ASSOCIATES (SEE HARD COPY FOR NAMES). BLOCK TO FOLLOW PROT SUBMIT 7/13/82. COSTANZI & ERSLEV FOLLOW PROT SUBMIT 9/10/82.

L Sep-29-82			82-20	DRS	111320
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REF SUBJECT INDA; SUBMIT NOTED FROM 6/23/82 MEETING WITH FDA.

L Oct-01-82			82-21	DRS	111323
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Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE	CL 232,315	ANTICANCER AGENT	

AMEND SUBJECT INDIA: PART IX, CHECKLIST & CV FOR ARLIN & CVs FOR ASSIST CLARKSON, GEE, KEMPKIN, MERTELSMANN, & STRAUS. ARLIN TO FOLLOW PROTOCOL SUBMIT 9/10/82.

L Cct-07-82 82-22 DRS 111347

AMEND SUBJECT INDIA: PART IX, CHECKLIST & CVs FOR WHITE, BITRAN, & AMARE, CVs FOR BILLINGS, DESSER, KOSLOFF, NEWMAN, ROBIN, SHAPIRO, & SWEET (ASSIST BITRAN), CVs FOR BODENSTEINER, COOK, LYNCH, & SKIKNE (ASSIST AMARE); PART X, AMEND TO PROT FOLLOWED BY SILVER, ALLEGRA, WOODCOCK, & PERLOFF. WHITE & BRITTAN TO FOLLOW PROT SUBMIT 7/13/82, AMAR FOLLOW PROT SUBMIT 9/10/82.

L Cct-18-82 82-23 DRS 111358

AMEND SUBJECT INDIA: PART IX, CHECKLIST & CVs FOR STARLING, MISER, MULNE, & MILLER, CV FOR FERNBACH, MAHONEY & STEUBER (ASSIST STARLING), CV FOR NEWTON, ROACH & RUYMANN (ASSIST MISER & MULNE), CV FOR HOFFMAN & TAN (ASSIST MILLER); PROTOCOL & CRF FOR MULTICENTER STUDY.

L Cct-25-82 82-24 DRS 111369

AMEND SUBJECT INDIA: PART IX, CHECKLIST FOR ADDITIONAL STUDY BY GAMS, CHECKLIST & CV FOR CASSELETH AND VATS, CV FOR THUEWORTHY (ASSIST VATS), UPDATED CV FOR GAMS. GAMS & CASSELETH TO FOLLOW PROTOCOL SUBMIT 9/10/82. VATS TO FOLLOW PROTOCOL SUBMIT 10/18/82.

L Nov-08-82 82-25 DRS 111402

AMEND SUBJECT INDIA: PART IX, CHECKLIST FOR 2nd MOORE STUDY (QUALIF SUBMIT 8/18/82); PART X, AMEND TO WEIDHART PROTOCOL SUBMIT 3/24/82, DER FOR 90TH LED AND NCI SPONSORED STUDIES. MOORE TO FOLLOW PROTOCOL SUBMIT 9/10/82.

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

L Dec-03-82			82-26	DRS	111461
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AMEND SUBJECT INDA: PART IX, CV FOR BERNHARDT
(ASSIST SILVER); PART X, ADDENDUM TO PROTOCOL
SUBMITTED 7/13/82.

L Dec-08-82			82-27	DRS	111465
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AMEND SUBJECT INDA: PART IX, CHECKLIST & CVS FOR
PETERSON & STEIN, CVS FOR BARNES, BLOOMFIELD,
HRUSHESKY, HURD, KENNEDY, KENYON, AND KIANG
(PETERSON ASSOC); PART X, PROTOCOL TO BE FOLLOWED
BY PETERSON & STEIN.

L Dec-13-82			82-28	DRS	111445
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AMEND SUBJECT INDA: PART IX, CV FOR DUKART TO
REPLACE FUIJIMORI AS LED MONITOR; PART X, AMEND TO
PROTOCOL SUBMITTED 6/7/82.

F Dec-29-82		TELEPHONE CALL DR. JOHNSON TO DR. B. J. CLARK (CONF 1/10/83)		DRS	830034
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(a) PROTOCOL
Questioned 1st line therapy for non-Hodgkins lymph

L Jan-04-83		AMENDMENT	83-1	DRS	830163
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(a) CV, CKLST
PT9 /003-046-006
DP3-46 SUBM 12/8/82, AMENDED 6/21/83
GAMS, RICHARD A
LYMPHOMA
NON-HODGKIN'S

AMEND SUBJECT INDA: PART IX, CHECKLIST & UPDATED
CV FOR GAMS. GAMS TO FOLLOW PROTOCOL SUBMITTED
12/8/82.

L Jan-10-83	F Dec-29-82	AMENDMENT RIVKIN STUDIES	83-2	DRS	830021
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Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

(b) PROTOCOL

PT10 /003-046-010

No patients on 1st line therapy

(c) PROTOCOL # /PT 10

DP 3-44 dosage amended, originally submitted
9/10/82

AMEND SUBJECT INDIA: PART IX, CHECKLIST FOR SILVER
THIRD STUDY, CV FOR 2 ADDITIONAL ASSOCIATES MOORE
AND WOLF; PART X, AMEND TO PROT SUBMIT 9/10/82.
SILVER TO FOLLOW PROT SUBMIT 10/8/82.

F Feb-04-83

6/7/82 MESTASTIC BREAST CA;12/8/82 NON-HODGKINS
LYMPH SUBMIS DRS 830135

(a) PROTOCOL

Exclude Novantrone as single agent w/non-Hodg lymph

(b) INVEST BROCH

2/82,pg116:clar elig,monit prior heart
dis,cardiomyopathy

REF APPLICATION FOR INDIA & LED CORRES 6/7 &
12/8/82. APPROVE INITIATION OF CLIN TRIALS. HAVE
FOLLOWING RECOMMENDATIONS: (1)IN PROT SUBMIT
12/8/82, SHOULD MODIFY TO EXCLUDE AS FIRST LINE
THERAPY, PAT WITH NON-HODGKINS LYMPHOMA, AND
(2)CLINICAL BROCHURE SHOULD STATE ELIGIBILITY
RESTRICTIONS REGARDING PRIOR HEART DISEASE.

L Feb-09-83

AMENDMENT 83-6 DRS 830130
SARTIANO/BODEY STUDIES

(a) CV(& ASSOCs),CKLST,PROT

PT9,10 /003-047-001

BODEY,GERALD P

(c) CKLST,CV-ASSOC(s)

/003-040-0

PROT SUBM 7/13/82

SARTIANO,GEORGE P

CA-BREAST; vs ADRIAMYCIN

MULTI-CTR 2nd LINE PTS

AMEND SUBJECT INDIA: PART IX, CHECKLIST FOR 2ND
SARTIANO STUDY, CHECKLIST FOR NEW BODEY STUDY.
UPDATED CV FOR BABCOCK (ASSOCIATE OF SRTIANO),
CVs FOR BURGESS, ESTEY, LEGHA, & VALDIVIESO
(ASSIST BODEY); PART X, PROTOCOL FOR BODEY STUDY.
SARTIANO TO FOLLOW PROTOCOL SUBMIT 7/13/82 AND
AMENDED 1/10/83.

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

L Feb-14-83

AMENDMENT 83-7 DRS 830124
KREMENTZ/VOGEL/HOLLAND/PLOTKIN/MUGGIA STUDIES

- (a) CKLST & PROTOCOL
PT9,10 /003-048-004
KREMENTZ, EDWARD T
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
- (b) CV, CKLST, PROTOCOL
PT9,10 /003-055-001
HOLLAND, JAMES F
ALL
COMBINED w/ VINCRISTINE & DEXAMETHASONE
- (c) CV, CKLST, PROTOCOL
PT9,10 /003-048-001
MUGGIA, FRANCO
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
- (d) CV, CKLST, PROTOCOL
PT9,10 /003-048-005
PLOTKIN, DAVID
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
- (e) CV, CKLST, PROTOCOL
PT9,10 /003-048-002
VOGEL, CHARLES L
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
- (f) CV # /PT 9
Assoc: Dr. Wang
- (g) CV # /PT 9
Assoc: Drs. Cuttner, Harris, Ohnuma, Paciucci
- (h) CV # /PT 9
Assoc: Drs. Carter, Sutherland
- (i) CV # /PT 9
Assoc: Drs. Blum, Bottino, Green, Levin, Speyer, Spiegel,
Wernz

AMEND SUBJECT INDA: PART IX, CHECKLIST FOR
KREMENTZ SECOND STUDY, CHECKLIST & CVs FOR VOGEL,
HOLLAND, PLOTKIN, AND MUGGIA, UPDATED CV FOR
CARTER & SUTHERLAND, CVs FOR VOGEL, HOLLAND &
MUGGIA ASSOCIATES (SEE HARD COPY FOR NAMES); PART
X, PROT FOR VOGEL, KREMENTZ, PLOTKIN, & MUGGIA
STUDIES, PROT FOR HOLLAND STUDY.

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

L Feb-24-83			83-8	DRS	111629
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AMEND SUBJECT INDA: PART IX, CHECKLIST AND CVs FOR BYRNE & JUSS, CV FOR WOOLLEY (ASSIST BYRNE), CVs FOR PASCHOLD, CAPONERA & POPE (ASSIST MUSS), CV FOR BRAICH (ASSIST JONES IN STUDY SUBMIT 1/25/83). BYRNE & MUSS TO FOLLOW PROTOCOL SUBMIT 2/14/83.

L Mar-02-83			83-9	DRS	111663
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AMEND SUBJECT INDA: PART IX, CHECKLIST & CV FOR DESAI, CV FOR DIMITROV TO ASSIST NEIDHART. DESAI WILL FOLLOW PROTOCOL SUBMIT 2/14/83. MULNE WILL BE ASSUMING RESPONSIBILITY FOR PROTOCOL STUDY SUBMIT 10/18/82 FOR WISER.

L Mar-04-83			83-10	DRS	111664
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AMEND SUBJECT INDA: PART IX, CVs FOR BODEY'S ASSISTANTS ON STUDY PROTOCOL SUBMIT 2/9/83 (REF HARD COPY LETTER FOR NAMES).

L Mar-07-83			83-11	DRS	111666
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AMEND SUBJECT INDA: PART IX, CHECKLIST & CVs FOR DECONTI & BRODOVSKY, CVs FOR BYRNE, DAVIS, FLATOW, HETZEL, ROSS, STEINGART, & WHITE (ASSIST DECONTI), CVs FOR LAUCIUS & HOLROYDE (ASSIST BRODOVSKY). DECONTI & BRODOVSKY TO FOLLOW PROTOCOL SUBMIT 2/14/83.

L Mar-17-83			83-12	DRS	111690
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AMEND SUBJECT INDA: PART IX, CHECKLIST FOR 3rd GOLOMB STUDY, CHECKLIST & CV FOR PAPISH & ASSOCIATES KRITZMAN, MIER, MILLER, PARKINSON, RUDDERS, & TAYLOR, CV FOR LESTER & VOGELZANG (ASSIST GOLMB). GOLOMB & PAPISH TO FOLLOW PROTOCOL SUBMIT 2/14/83. ACKNOWL RECEIPT FDA 2/4/83 LETTER AND IMPLEMENTING RECOMMENDATIONS MADE.

Led/ FDA	Event Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp	Event Due	Event ID
16,332	IND	MITOXANTRONE	CL 232,315 ANTICANCER AGENT				

L Mar-22-83				83-13	DRS		111701
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AMEND SUBJECT INDA: PART IX, CHECKLIST SHOWING NEW STUDY FOR GAMS & CV FOR ASSOCIATES PERLMAN AND KARDINAL. GAMS TO FOLLOW PROTOCOL SUBMIT 2/14/83.

L Mar-31-83				83-14	DRS		111715
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AMEND SUBJECT INDA: PART IX, CHECKLIST & CVs FOR BENNETT & DOROSHOW, CV FOR BAKEMEIER, CARIGNAN, & MCCUNE (ASSIST BENNETT), CV FOR BERTRAND, BROWNING, CARR, & OVERBY (ASSIST DOROSHOW), CHECKLIST SHOWING ADDRESS CHANGE FOR ARLIN, UPDATED CV FOR ARLIN. BENNETT & DOROSHOW TO FOLLOW PROTOCOL SUBMIT 2/14/83.

L Apr-06-83				83-15	DRS		111750
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AMEND SUBJECT ANDA: PART IX, CHECKLIST FOR HOLLAND 2ND STUDY; PART X, PROTOCOL FOR HOLLAND NEW STUDY.

L Apr-22-83			AMENDMENT	83-16	DRS		830226
			PROTOCOL SUPPLEMENT TO GAM'S STUDY IN ADULT LEUKEMIA				

AMEND SUBJECT INDA: PART X, PROTOCOL SUPPLEMENT TO GAM STUDY SUBMIT 9/10/82.

L May-11-83			AMENDMENT	83-17	DRS		830285
			SCHEIN ASSISTING BYRNE IN STUDY FILED 2/24/83				

AMEND SUBJECT INDA: PART IX, CV FOR SCHEIN TO ASSIST BYRNE IN STUDY FILED 2/24/83.

L May-27-83			AMENDMENT	83-18	DRS		830343
			BERTINO/BENNETT STUDIES				

L Jun-13-83			AMENDMENT	83-19	DRS		830382
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Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(a) PROG RPT & CKLST # /PT 9,10			
L Jun-15-83		AMENDMENT MULTICTR NON-HODGKIN'S LYMPH STUDY	83-20	DRS	830433
		(a) CKLST # /PT 9 ERSLEV, ALLAN J			
L Jun-21-83		AMENDMENT AMEND TO MULTICTR NON-HODGKIN'S LYMPHOMA PROTO SUB 12/8/82	83-21	DRS	830483
L Jun-24-83		AMENDMENT	83-22	DRS	830496
L Jun-29-83		AMENDMENT HENDERSON STUDY	83-23	DRS	830502
L Jul-06-83		AMENDMENT	83-24	DRS	830560
		(a) DRUG EXPER RPT # /PT 10 NCI-Sponsored Study			
L Jul-25-83		AMENDMENT	83-25	DRS	830628
		(a) CV, CKLST # /PT 9 MULTI-CENTER BREAST CANCER PROTOCOL SUBMT'D 2/14/83 MORGAN, LEE ROY CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO) CYCLOPHOSPHAMIDE-N-5FU vs CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU			
L Jul-29-83		AMENDMENT CV'S VARIOUS ASSTS; HOLLAND STUDY	83-26	DRS	830635
		(a) PROTOCOL PT 9,10 /003-065-001 HOLLAND, JAMES F LYMPHOMA COMBINED w/ VINCRISTINE & DEKAMETHASONE			
L Aug-08-83		AMENDMENT	83-27	DRS	830645

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(a) CV & PROTOCOL # /PT 9 PROTOCOL SUBM 7/29/83 HOLLAND, JAMES F			
		(b) CV & PROTOCOL # /PT 9 7/29/83 SUBM CORRECTION: CV SUBM 3/31/83; STUDYING AC LEUKEM			
L Aug-09-83		AMENDMENT	83-28	DRS	830646
		(a) CV # /PT 9 DR GAMS' ASSISTANTS IN BREAST CA STUDY			
		(b) INVEST SITE ADDITIONAL SITE FOR AC MYELOBLASTIC LEUKEMIA STUDY WIERNIK, PETER H LEUKEMIA			
L Aug-12-83		AMENDMENT	83-29	DRS	830654
		MULTICENTER BREAST CA STUDY			
		(a) CV # /PT 9 ASS'T TO DR J. EVERETT			
L Aug-17-83		AMENDMENT	83-30	DRS	830663
		(a) CKLST /003-048-0 REPLACES DECONTI; PROT 3-48 SUBM 2/14/83; CV SUBM 3/7/83 WHITE, CHARLES F CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO) CYCLOPHOSPHAMIDE-N-5FU vs CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU			
		(b) PROTOCOL EMERGENCY TREATMENT BESIDES FORMAL STUDY			
		(d) CV-ASSOC(s) /003-048-0 test ??? MUST WE HAVE INDIVIDUAL RR6-RR7 RECORDS FOR EACH??			
L Aug-26-83		AMENDMENT	83-31	DRS	830698
		(a) PROTOCOL # /PT 10 AMEND TO AC MYELOBL LEUK PROT SUBMD 4/6/83			
		(b) PROTOCOL AMEND TO REFRACTORY LYMPHOMA STUDY SUBMITTED 7/29/83			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
L Aug-30-83		AMENDMENT	83-32	DRS	830692
		(a) CV(& ASSOCS),CKLST PT9 /003-040-025 PROT SUBM 7/13/82, AMENDED 1/10/83 BERNARD,STEPHEN A CA-BREAST; vs ADRIAMYCIN MULTI-CTR 2nd LINE PTS			
L Sep-07-83		AMENDMENT	83-33	DRS	830705
		(a) FORMULA # /PT 3 (b) MONOGRAPH # /PT 5 CONTROLS (c) STABILITY # /PT 5 (d) LABEL # /PT 7 (d) LABEL # /PT 7 (e) CV # /PT 9 ASSISTANTS TO DRS R GAMS, E KREMENTZ			
L Sep-12-83		AMENDMENT		DRS	830732
		(a) CV CV'S FOR DR DENNETT'S ASSOCIATES			
L Sep-14-83		CORRESPONDENCE REQUEST 1-A IND/NDA CLASSIFICATION		DRS	830736
		(a) SUMMARY NOTES FROM 5/3/83 LED-FDA MTG: MTX'S ADVNTGS OVER EXIST THER (b) SUMMARY DR CLARK PROFILE OF MTX: SAF/EFFIC IN TREATING ADV BREAST CA			
L Oct-06-83		AMENDMENT	83-36	DRS	830785
		(a) CV # /PT 9 CV FOR DR BODEV'S NEW ASST -FORMER CDINVSCTR,DR YAP, LEAVES			
L Oct-10-83		AMENDMENT	83-37	DRS	830787
		(a) CV,CKLST CV'S FOR DR ARLIN & ASSOC'S. ADD'L ASSOC CV SUBM 3/31/83			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		ARLIN, ZALMEN A. CA-BREAST; vs ADRIAMYCIN MULTI-CTR 2nd LINE PTS			
L Oct-20-83		AMENDMENT PART 10-AMNDMT TO PHASE I-II PROT (DP 3-55) SUBM 2/14/83	83-38	DRS	830815
L Oct-25-83		AMENDMENT ADD'L PRE-CLINICAL STUDIES, PART 6	83-39	DRS	830828
L Oct-28-83		AMENDMENT (a) CV, CKLST # /PT 9 CKLST FOR DR ELLISON (CV SUBM 10/6/83) & CV'S FOR HER ASSOCS (b) CV # /PT 9 DR TESTER (DR LEVICK'S ASSOC); DR GREENBERG (BLOCK'S ASSOC) (c) SUMMARY # /PT 9 DR ELLISON REPLACES DR PERLOFF (LEFT) AS PRINC INVSCTR	83-40	DRS	830840
L Oct-31-83		CORRESPONDENCE REQUEST COMMENTS ON PROSPECTIVE PROTOCOLS(2) & CLIN STRATEGY	83-41	DRS	830843
L Nov-02-83		AMENDMENT (a) CV, CKLST, PROTOCOL PT9 /003-000-000 WEINER, MARTIN J	83-42	DRS	830853
L Nov-09-83		AMENDMENT (a) PROTOCOL # /PT 10 REVISIONS (SECTNS 4.25 & 6.52) TO DR BODEV'S PROT SUB 6/7/82	83-43	DRS	830867
L Nov-11-83		AMENDMENT (a) CKLST, CV-ASSOC(s) PT9a /003-048-009 DP 3-48 SUBM 2/14/83, AMND' 2/28/84; CV SUB 4 3/17/83	83-44	DRS	830875

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		PARKINSON, DAVID R CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO) CYCLOPHOSPHAMIDE-N-5FU vs CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU (c) PROTOCOL /003-044-0 BERTINO'S CV AND CKLST SUBM 5/27/83; ONE PT-COMPASSION BASIS BERTINO, JOSEPH LEUKEMIA			
L Nov-30-83		AMENDMENT	83-45	DRS	830903
		(a) CKLST PT9a /003-048-017 PROT SUBM 2/14/83; CV's SUBM 7/13/82 WOLFF, STEVEN N CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO) CYCLOPHOSPHAMIDE-N-5FU vs CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU (b) CV # /PT 9b CV's FOR 3 ASSOC'S OF DR R GAMS (#34) UNDER PROT SUB 2/14/83			
L Dec-02-83		AMENDMENT	83-46	DRS	830912
		(a) CV, CKLST, PROTOCOL PT9,10 /003-070-000 CV FOR DR JONES. HIS 3 ASSOCS' CV's WERE FILED 2/14/83 JONES, ROY CA-BREAST; DOSE RANGING ESCALATING DOSE -CARDIAC MEASUREMENTS			
L Dec-12-83		CORRESPONDENCE UPDATED CARDIOTOX RPT TO SUPPORT REQUEST FOR 1A IND/NDA CLAS	83-47	DRS	830930
L Dec-13-83		AMENDMENT	83-48	DRS	830932
		(a) CKLST, PROT PT9a,10 /003-072-001 CV SUBM 7/22/82 HENDERSON, I CRAIG CA-BREAST; SPECIAL-PK INFLUENCE OF HEPATIC FUNCTION			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(b) CV,CKLST,INVEST AGREE # /PT 9b DR ARLIN(#85) TO FOLLOW THE MULTI-CTR BR CA PROT SUB 2/14/83			
L Dec-19-83		AMENDMENT	83-49	DRS	830943
		(a) CKLST # /PT 9 CL FOR DR QAZI(CV FILED 7/29/83);SUBBING FOR DR BENNETT,#111			
L Jan-04-84		AMENDMENT	84-1	DRS	831034
		(a) CV # /PT 9 CVs FOR 2 ASSOCS OF DR BERTINO (#113) FOR PROT SUBM 11/11/83			
L Jan-20-84		AMENDMENT	84-2	DRS	831068
		(a) INVEST BROCH # /PT 7 ADDENDUM TO 6/7/82 BROCHURE; RE: CARDIOTOXICITY			
		(b) CV(& ASSOCS),CKLST PT9 /003-048-019 PROTO SUBM 2/14/83 GEORGE,SEBASTIAN CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO) CYCLOPHOSPHAMIDE-N-5FU vs CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU			
F Jan-23-84		CORRESPONDENCE		GRP	831073
		REQUEST INFO ON POSSIBLE CAUSES & REMEDIES OF PRECIPITAION			
L Jan-31-84	B Dec-21-83	CORRESPONDENCE	84-3	DRS	831095
		SUMMARY/NOTES OF PRE-NDA DISCUSSION --FOR FDA REVIEW			
L Feb-01-84		AMENDMENT	84-4	DRS	831106
		(a) CKLST /003-048-0 PROT SUBM 2/14/83; CV(& ASSOCS) SUBM 8/30/83 BERNARD,STEPHEN A CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO) CYCLOPHOSPHAMIDE-N-5FU vs CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTHONE	CL 232,315	ANTICANCER AGENT	
L Feb-14-84		AMENDMENT	84-5	DRS	831144
		(a) CV,CKLST,INVEST AGREE # /PT 9a DR WEIDEN(#124) WILL FOLLOW MULTI-CTR BR CA PROT SUB 2/14/83			
L Feb-21-84		AMENDMENT	84-6	DRS	831156
		(a) CKLST,PROT PT9a,10 /003-071-001 CV SUBM 1/25/83 CASE,DELVYN C LYMPHOMA; vs m-BACOD m-BNCOD COMBO			
		(b) CKLST,PROT PT9a,10 /003-074-001 CV SUBM 1/25/83 CASE,DELVYN C ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
L Feb-22-84		AMENDMENT	84-7	DRS	831160
		(a) DEAR INVESTIGATOR LETTER # /PT 7 WARNING TO READ LABELS CAREFULLY; OD(DEATHS) AT FOREIGN HOSP			
		(b) DEAR PHARMACIST LETTER # /PT 7 WARNING TO READ LABELS CAREFULLY; OD(DEATHS) AT FOREIGN HOSP			
		(c) CV,CKLST,PROTO PT9,10 /003-075-001 UPDATED CV ALBERTS,DAVID S CA-OV,COLON; DOSE RANGING PK OF IP ADMINISTRATION			
F Feb-23-84	L Feb-23-84	ADVERTISING		ECM	831153
		TORONTO TELECONFERENCE SEEN AS PROMOTION OF UNAPPROVED DRUG			
L Feb-28-84		AMENDMENT	84-8	DRS	831166
		(a) CV,CKLST,INVEST AGREE # /PT 9a,c DR CONRAD(#125) WILL FOLLOW MULT-CTR BR CA PROT SUPM 2/14/83			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(b) CV,CKLST,INVEST AGREE # /PT 9b,c DR CHLEBOWSKI(#60;2nd STUDY) TO FOLL ADV BR CA PROT 12/13/83			
		(c) PROTOCOL AMNDMT TO MULTI-CTR CR CA PROT SUBM 2/14/83			
L Mar-05-84		AMENDMENT	84-9	DRS	831266
		(a) CKLST PT9a /003-071-003 PROT SUBM 2/21/84; CV SUBM 10/10/83 ARLIN,ZALMEN A LYMPHOMA; vs m-BACOD m-BNCOD COMBO			
		(b) CKLST PT9a /003-074-002 PROT SUBM 2/21/84; CV SUBM 10/10/83 ARLIN,ZALMEN A ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
L Mar-20-84		AMENDMENT	84-10	DRS	831289
		(a) CV,CKLST PT9a /003-071-002 DP 3-71 SUBM 2/21/84 MABRY,R JAMES LYMPHOMA; vs m-BACOD m-BNCOD COMBO			
		(b) CV,CKLST PT9a /003-071-004 DP 3-71 SUBM 2/21/84 COHEN,RICHARD J LYMPHOMA; vs m-BACOD m-BNCOD COMBO			
L Mar-21-84		AMENDMENT	84-11	DRS	831290
		(a) CV # /PT 9 CV's FOR DRs ALVAREZ & RODRIGUES, DR ARLIN'S(#85) ASSISTANTS			
L Mar-27-84		AMENDMENT	84-12	DRS	831300
		(a) CV,CKLST PT9a /003-048-024 DP 3-48 SUBM 2/14/83, AMENDED 2/28/84			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

PRESANT,CARY A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

(b) CV,CKLST
PT9b /003-048-023
DP 3-48 SUBM 2/14/83, AMENDED 2/28/84
TRUMP,DONALD L

CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

(c) CV,CKLST
PT9b /003-048-025
DP 3-48 SUBM 2/14/83, AMENDED 2/28/84
DENEFRIO,JOHN M

CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

L Mar-30-84

AMENDMENT 84-13 DRS 931302

(a) CKLST
PT9a /003-071-008
DP 3-71 SUBM 2/21/84; CV SUBM 1/25/83

(b) CV,CKLST
PT9b /003-071-005
DP 3-71 SUBM 2/21/84
DRESDNER,DAVID M

LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

(c) CV,CKLST
PT9b /003-071-007
DP 3-71 SUBM 2/21/84
BLUMING,AVRUM Z

LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

(d) CV,CKLST /003-074-0

DP 3-74 SUBM 2/21/84
DRESDNER,DAVID M
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)

L Mar-30-84

F Jan-23-84

CORRESPONDENCE 84-14 GRP 931310
BUFFERED BISULFITE-FREE FORMULA^N HAS REPLACED
FORMER FORM^N

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact -----	Resp Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT				
L Apr-02-84		AMENDMENT	84-15	DRS		831334
		(a) CKLST PT9a /003-071-006 MUL-CTR COMB REGIMEN PROT SUBM 2/21/84; CV SUBM 7/13/82 WOODCOCK, THOMAS M LYMPHOMA; vs m-BACOD m-BNCOD COMBO				
L Apr-09-84		AMENDMENT	84-16	DRS		831347
		(a) CKLST, CV-ASSOC(s) PT9a /003-048-026 PROT SUBM 2/14/83, AMENDED 2/28/84; CV SUBM 7/13/82 GRACE, WILLIAM R CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO) CYCLOPHOSPHAMIDE-N-5FU vs CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU				
		(b) PROTOCOL # /PT 10 AMNDMT TO HEPATOMA PROT SUBM 6/11/82 (DR R CHLEBOWSKI #60)				
F Apr-11-84	L Sep-14-83	NOT APPROVABLE REQUEST FOR 1A CLASSIFICATION DENIED		DRS		831351
L Apr-16-84		AMENDMENT	84-17	DRS		831360
		(a) CV, CKLST PT9abc /003-071-012 DP 3-71 SUBM 2/21/84 ABBRUZZESE, JAMES L LYMPHOMA; vs m-BACOD m-BNCOD COMBO				
		(b) CV, CKLST PT9abc /003-071-009 DP 3-71 SUBM 2/21/84 GOODMAN, GARY E LYMPHOMA; vs m-BACOD m-BNCOD COMBO				
		(c) CV, CKLST PT9abc /003-071-013 DP 3-71 SUBM 2/21/84				

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		HOLROYDE, CRISTPHER P LYMPHOMA; vs m-BACOD m-BNCOD COMBO			
		(d) CKLST PT9abc /003-071-010 DP 3-71 SUBM 2/21/84; STEIN'S (2nd STUDY) CV SUBM 12/8/82 STEIN, RICHARD S LYMPHOMA; vs m-BACOD m-BNCOD COMBO			
		(e) CKLST PT9abc /003-071-011 DP 3-71 SUBM 2/21/84; CV SUBM 7/13/82 WOLFF, STEVEN N LYMPHOMA; vs m-BACOD m-BNCOD COMBO			
L Apr-19-84		AMENDMENT	84-18	DRS	831369
		(a) CKLST PT9a /003-072-003 3-72 SUBM 12/13/83; CV SUBM 7/13/82 WOODCOCK, THOMAS M CA-BREAST; SPECIAL-PK INFLUENCE OF HEPATIC FUNCTION			
L Apr-23-84		AMENDMENT	84-19	DRS	831370
		(a) CV CVs FOR 3 ASSTs OF DR D SPICER (#71)			
L Apr-30-84		AMENDMENT	84-20	DRS	831379
		(a) CKLST PT9a /003-071-014 PROT SUBM 2/21/84; CV(& ASSOCs) SUBM 3/31/84 BENNETT, J/OAZI, RAMAN LYMPHOMA; vs m-BACOD m-BNCOD COMBO			
		(b) CV(& ASSOCs), CKLST PT9b /003-074-004 PROT SUBM 2/21/84 GROPPE, CARL W ANLL; vs CEPURIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C) (CYTARABINE)			
		(c) CV-ASSOC(s) PT9c /003-071-011 BERMAN, LEVINE, STREETER, RASSIGA			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

L May-02-84

AMENDMENT

84-21

DRS

831408

- (a) CKLST
PT9 /003-071-016
PROT SUBM 2/21/84; CV SUBM 2/28/84
CONRAD, MARCEL E
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

L May-04-84

AMENDMENT

84-22

DRS

831415

DR KRAKOFF REPLACES DR BODEY(#100) AS PRINCIPLE
INVESTIGATOR

- (a) CV,CKLST
PT9 /003-041-001
KRAKOFF REPL BODEY AS PRIN INV; DP3-41 SUBM 6/7/82
KRAKOFF, I H
CA-BREAST
COMB w/ CYCLOPHOS, 5-FU X-OVER TO
ADRIAMYCIN/VINBLASTINE
- (b) CV(& ASSOCS),CKLST
PT9 /003-071-015
DP3-71 SUBM 2/21/84
SHAW, JOHN
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (c) CV,CKLST
PT9 /003-047-001
KRAKOFF REPL BODEY AS PRIN INV; DP3-47 SUBM 2/9/83
KRAKOFF, I H
- (d) INVESTIGATOR REPLACEMENT /003-041-0
BODEY REPLACED BY KRAKOFF
BODEY, GERALD P
CA-BREAST
COMB w/ CYCLOPHOS, 5-FU X-OVER TO
ADRIAMYCIN/VINBLASTINE
- (e) INVESTIGATOR REPLACEMENT /003-047-0
BODEY REPLACED BY KRAKOFF
BODEY, GERALD P

L May-22-84

AMENDMENT

84-23

DRS

831449

- (a) CV(& ASSOCS),CKLST
PT9a,d /003-048-027
DP3-48 SUBM 2/14/83, AMND 2/29/84; UPDATED CV

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE	CL 232,315	ANTICANCER AGENT	

OISHI, NOBORU
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

(b) CKLST
PT9b,c /003-071-018
DP3-71 SUBM 2/21/84; CV(& ASSOCS) SUBM 9/3/82
DOTY, GORDON L
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

(c) CV, CKLST
PT9b,c /003-071-017
DP3-71 SUBM 2/21/84; ASSOCS* CVs SUBM 3/27/84
KENNEDY, PETER S
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

(d) CV(& ASSOCS), CKLST
PT9b,c /003-071-019
DP3-71 SUBM 2/21/84
GABRIEL, DON A
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

(e) CV(& ASSOCS), CKLST
PT9b,c /003-071-012
DP3-71 SUBM 2/21/84
LEVINE, JAMES D
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

(f) CV(& ASSOCS), CKLST
PT9b,c /003-071-020
DP3-71 SUBM 2/21/84
SCOTT, ROBERT B
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

(g) INVESTIGATOR REPLACEMENT /003-071-0
ABRUZZESE REPLACED BY LEVINE
ABRUZZESE, JAMES L
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

L May-23-84

AMENDMENT

84-24

DRS

931463

(a) CV, CKLST
PT9a /003-000-000
DP3-48 SUBM 2/14/83, AMND 2/28/84; ONE
PT, COMPASSIONATE, OL

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTHONE CL 232,315 ANTICANCER AGENT

- (b) SAMUELS, ARTHUR J
CV, CKLST
PT9a /003-048-028
PROT SUBM 2/21/84
BENIGNO, BENEDICT R
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
(c) CV (& ASSOCS), CKLST
PT9a /003-071-021
DP3-71 SUBM 2/21/84
FASS, LEROY
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

L May-30-84 AMENDMENT 84-25 DRS 831481

- (a) CV, CKLST
PT9 /003-074-005
MULTICTR COMBO REGIMEN ACUTE NONLYMPH LEUK PROT
SUBM 2/21/84
TRANUM, BILL L
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C) (CYTARABINE)

L May-31-84 AMENDMENT 84-26 DRS 831480

- (a) CKLST # /PT 9
CURRENTLY ACTIVE INVESTIGATORS
(b) PROGRESS RPT # /PT 10
ALBERTS, DAVID S
CA-DV, COLON; DOSE RANGING
PK OF IP ADMINISTRATION
ARLIN, ZALMEN A
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C) (CYTARABINE)
ARLIN, ZALMEN A
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
BERNARD, STEPHEN A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
BERNARD, STEPHEN A
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTHONE	CL 232,315	ANTICANCER AGENT	

BERTINO, JOSEPH
LEUKEMIA

CASE, DELVYN C
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C) (CYTARABINE)

CASE, DELVYN C
LYMPHOMA

NON-HODGKIN'S

CASE, DELVYN C

LYMPHOMA; vs m-BACOD

m-BACOD COMBO

DENEFRIO, JOHN M

CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)

CYCLOPHOSPHAMIDE-N-5FU vs

CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

DENEFRIO, JOHN M

CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)

CYCLOPHOSPHAMIDE-N-5FU vs

CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

GAMS, RICHARD A

LYMPHOMA

NON-HODGKIN'S

GOLOMB, HARVEY M

LYMPHOMA

NON-HODGKIN'S

GRACE, WILLIAM R

CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)

CYCLOPHOSPHAMIDE-N-5FU vs

CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

GRACE, WILLIAM R

CA-BREAST; vs ADRIAMYCIN

MULTI-CTR 2nd LINE PTS

HENDERSON, I CRAIG

CA-BREAST; SPECIAL-PK

INFLUENCE OF HEPATIC FUNCTION

HOLLAND, JAMES

HOLLAND, JAMES F

ALL

COMBINED w/ VINCRISTINE & DEXAMETHASONE

HOLLAND, JAMES F

LYMPHOMA

COMBINED w/ VINCRISTINE & DEXAMETHASONE

JONES, ROY

CA-BREAST; DOSE RANGING

ESCALATING DOSE -CARDIAC MEASUREMENTS

Led/ Event FLA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp Event ----- Due ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT		

JONES,STEPHEN E
LYMPHOMA
NON-HODGKIN'S
KRAKOFF,IR /RODEV
KREMENTZ,EDWARD T
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
MORGAN,LEE ROY
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
MUGGIA,FRANCO
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
PARKINSON,DAVID R
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
PLOTKIN,DAVID
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
PRESANT,CARY A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
RIVKIN,SAUL E
LYMPHOMA
NON-HODGKIN'S
SCHWARTZ,I ROBERT
LEUKEMIA

SEBASTIAN,GEORGE
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
SILVER,RICHARD T
LYMPHOMA
NON-HODGKIN'S
STUART,JOHN J
LYMPHOMA
NON-HODGKIN'S
TRUMP,DONALD L
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp Event ----- Due ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT		

VOGEL, CHARLES L
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WHITE, CHARLES F
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WOLFF, STEVEN N
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WOODCOCK, THOMAS M
CA-BREAST; SPECIAL-PK
INFLUENCE OF HEPATIC FUNCTION
WOODCOCK, THOMAS M
CA-BREAST; SPECIAL-PK
INFLUENCE OF HEPATIC FUNCTION

L Jun-06-84 AMENDMENT 84-27 DRS 831531

- (a) CKLST
PT9acd /003-071-023
DP3-71 SUBM 2/21/84; CV SUBM 10/7/82
BITRAN, JACOB
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (b) CKLST
PT9acd /003-071-025
DP3-71 SUBM 2/21/84; CV SUBM 9/10/82
BROWN, CORONWY O
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (c) CV, CKLST
PT9acd /003-071-024
DP3-71 SUBM 2/21/84
STONE, LAWRENCE A
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (d) CV, CKLST
PT9acd /003-071-022
DP3-71 SUBM 2/21/84
VOYCE, GARY F
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (e) CV, CKLST, PROTO, INVES AGR
PT9b /003-074-006
ADDL STUDY BY DR GAMS; CV SUBM
1/4/83; PROT(3-74) SUBM 2/21/84

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

L Jun-14-84 AMENDMENT 84-28 DJF 931543
IN REFERENCE TO DR NEIDHART'S (#56) BREAST CA STUDY
(3-43-1)

- (a) CASE REPORT FORM
GLOSSARY OF ABBREVIATIONS/CODES (FOR CRFs) PREPARED BY
OSU CA CTR

L Jun-15-84 AMENDMENT 84-29 DRS 931545

- (a) CKLST
PT9a /003-071-014
CV SUBM 7/29/83; DP3-71 SUBM 2/21/84; QAZI CO-INV
W/ BENNETT
QAZI, RAMAN
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

L Jun-19-84 AMENDMENT 84-30 DRS 931561

- (a) CKLST
PT9acd /003-071-028
DP3-71 SUBM 2/21/84; CV(& ASSOCS) SUBM
1/4/83, 6/6/84
GAMS, RICHARD A
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (b) CKLST
PT9acd /003-071-029
DP3-71 SUBM 2/21/84; CV(& ASSOCS) SUBM 6/24/83
WIERNIK, PETER H
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (c) CV(& ASSOCS), CKLST
PT9acd /003-071-026
(3-71) SUBM 2/21/84
HEIM, WILLIAM J
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (d) CV, CKLST
PT9acd /003-071-027
(3-71) SUBM 2/21/84
WACHI, DENNIS H
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(e) CKLST PT9acd /003-072-004 DP3-72 SUBM 12/13/83; CV(& ASSOCS) SUBM 10/10/83 APLIN,ZALMEN A CA-BREAST; SPECIAL-PK INFLUENCE OF HEPATIC FUNCTION			
		(f) CV(& ASSOCS),CKLST PT9acd /003-074-007 DP3-74 SUBM 2/21/84 ABRAMSON,NEIL ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
		(g) CV,CKLST PT9acd /003-074-006 DP3-74 SUBM 2/21/84 VILLA,LUIS ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
		(h) CKLST PT9acd /003-074-008 DP3-74 SUBM 2/21/84; CV(&ASSOCs) SUBM 6/24/83 WIERNIK,PETER H ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
L Jun-22-84		AMENDMENT	84-31	DRS	831566
		(a) CV,CKLST PT9a /003-074-009 DP3-74 SUBM 2/21/84 HICKS,WILLIAM J ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
L Jul-02-84		AMENDMENT	84-32	DRS	831667
		(a) CKLST PT9a /003-071-030 PROT 3-71 SUBM 2/21/84; CV(& ASSOCS) SUBM 7/13/82, 2/3/83 SILVER,RICHARD T LYMPHOMA; vs m-BACOD m-BNCOO COMBO			
		(b) CV,CKLST PT9b /003-043-001 POACH REPL NEIDHART(456) AS PRIN INV IN DP 3-43 SUBM 8/24/82			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE	CL 232,315	ANTICANCER AGENT	
		(c) RDACH, RALPH W PROTOCOL /003-000-0 QAZI FOLLOWING (BUT NOT PART OF) DP3-48 SUBM 2/14/83 QAZI, RAMAN			
L Jul-12-84		AMENDMENT	84-33	DRS	831691
		(a) CKLST PT9a /003-071-031 PROT 3-71 SUBM 2/21/84; CV SUBM 3/7/83 WHITE, CHARLES F LYMPHOMA; vs m-BACOD m-BNCOD COMBO			
		(b) CKLST PT9b /003-040-009 HESKETH REPL LOPEZ AS PRN INV; DP3-40 SUB 7/13/82; CV-4/30/84 HESKETH, PAUL /LOPEZ CA-BREAST; vs ADRIAMYCIN MULTI-CTR 2nd LINE PTS			
		(c) CV, CKLST PT9b /003-048-029 PROT 3-48 SUBM 2/14/83, AMENDED 2/28/84 PORTLOCK, CAROL S CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO) CYCLOPHOSPHAMIDE-N-5FU vs CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU			
L Jul-13-84		AMENDMENT	84-34	DRS	831692
		(a) CV # /PT 9 CVs FOR 3 ASSTs UNDER DR GRACE (#63; 3-40-3 -SUBM 7/13/82)			
L Jul-20-84		AMENDMENT	84-35	DRS	831702
		(a) CV # /PT 9 CVs FOR 5 ASSTs TO TRUMP (#128; 3-48-23); 3-48 SUBM 2/14/83			
L Jul-23-84		AMENDMENT	84-36	DJF	831711
		DER FROM DR DAO'S TRIAL (3-40-16) -MULTI-CTR BR CA PROT 3-40			
		(a) DRUG EXPER RPT # /PT 10 PT #3018 (AGE:30yrs) AMENORRHEA, HOT FLASHES			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOKANTHONE	CL 232,315	ANTICANCER AGENT	

L Jul-26-84		AMENDMENT	84-37	DJF	831705
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- (a) CKLST
PT9a /003-071-033
PROT 3-71 SUBM 2/21/84; ARMENTROUT'S CV SUBM
9/10/82
ARMENTROUT, STEVEN
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (b) CV,CKLST
PT9a /003-071-032
PROT 3-71 SUBM 2/21/84;
JAFFREY, IRA S
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (c) CV-ASSOC(s)
PT9c /003-071-028
11 ASSOCS TO GAMS (PROT SUBM 2/21/84)

L Jul-27-84	L Jul-13-84	CORRESPONDENCE		DJF	831742
		7/13/84 COVER LTR SHOULD HAVE READ 16,332 & NOT 17,560			

L Jul-30-84		AMENDMENT	84-38	DJF	831740
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- (a) CV,CKLST
PT9 /003-074-010
DP3-74 SUBM 2/21/84
WEINTRAUB, LEWIS R
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)

L Aug-06-84		AMENDMENT	84-39	DJF	831756
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- (a) CKLST
PT9a /003-074-012
DP3-74 SUBM 2/21/84; CV(& ASSOCS) SUBM 9/3/82
DOTY, GORDON L
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
- (b) CV,CKLST
PT9b /003-071-034
DP3-71 SUBM 2/21/84
DOSIK, MICHAEL H
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

L Aug-07-84

AMENDMENT

84-40

DJF

831763

- (a) CKLST
PT9a /003-071-023
DESSER (CV-10/7/82) REPLACES BITRAN AS PR INV FOR
3-71-23
BITRAN, JACOB
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
DESSER, R K /BITRAN
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
- (b) CV-ASSOC(s) # /PT 9b
4 ASSOCS OF DR H GOLOMB FOR 2 BR CA STUDIES
-3-40-21, 3-48-21

L Aug-14-84

AMENDMENT

84-41

DJF

831774

- (a) CV, CKLST, PROTO
PT9, 10 /003-069-001
UPDATED CV
MOORE, JOSEPH O
CA-LUNG
WITH CIS-PLATINUM IN ADENO CA OR LARGE CELL CA

L Aug-15-84

MEETING

84-42

DJF

831777

REQUEST MTG SEPT 24-26: ACUTE LEUKEMIA &
NON-HODGKIN'S LYMPH

L Aug-16-84

AMENDMENT

84-43

DJF

831812

- (a) CKLST
PT9a /003-074-011
3-74 SUBM 2/21/84; CV(& 13 ASSOCS) SUBM 1/4/83,
6/6, 7/26/84
GAMS, RICHARD A
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C) (CYTARABINE)
- (b) CV-ASSOC(s)
PT9b /003-048-008
FOR 2 ASSTs TO DR BRODOVSKY (#109 -3/7/83) IN
STUDY 3-48-8
- (c) CV-ASSOC(s)
PT9b /003-048-007
1 ASST TO DR HOLROYDE (#134 -4/16/84) IN STUDY
3-71-13

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

- (d) CV-ASSOC(s)
PT9c /003-048-007
- (d) CV-ASSOC(s)
PT9c /003-071-031
- (e) CV-ASSOC(s)
PT9d /003-048-023
FOR 8 ASSTs

L Aug-23-84		AMENDMENT	84-44	DJF	831825
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- (a) DEAR INVESTIGATOR LETTER # /PT
7
TO ALL ACTIVE INVS: AMENORRHEA IN PTS BEING
TREATED W/ MITOX

L Aug-24-84		AMENDMENT	84-45	DJF	831829
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- (a) ALL INVSTGTRS (EXCEPT HEIM) WILL FOLLOW 3-74 SUBM
2/21/84
- (b) CKLST
PT9b /003-074-016
DP3-74 SUBM 2/21/84; CV(& ASSOCS) SUBM
5/22/84, 8/30/83
GABRIEL, DON A
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
- (c) CKLST
PT9a /003-074-017
DP3-74 SUBM 2/21/84; CV(& ASSOCS) SUBM
7/13/82, 2/3/83
SILVER, RICHARD T
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
- (d) CV(& ASSOCS), CKLST
PT9c /003-074-015
DP3-74 SUBM 2/21/84
DOSIK, HARVEY
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
- (e) CV(& ASSOCS), CKLST
PT9c /003-074-014
DP3-74 SUBM 2/21/84
KLOSS, ROBERT A
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)

Led/ Event FIA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(f) CV(& ASSOCS),CKLST PT9c /003-074-013 DP3-74 SUBM 2/21/84 ROBINSON,WILLIAM ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
		(g) CV-ASSOC(s) PT9d /003-071-026 FOR 1 ASST TO DR HEIM (#150 -6/19/84) IN STUDY 3-71-26			
L Aug-30-84		AMENDMENT	84-46	DJF	831835
		(a) CV-ASSOC(s) # /PT 9 1 ASST TO DR WHITE(#116 -8/17/83); PROT 3-48 SUBM 2/14/83			
		(b) DRUG EXPER RPT # /PT 10 STUDY 3-48-8 (PT: EP #4102): HYPOTENSION			
L Sep-05-84		AMENDMENT	84-47	DJF	831852
		(a) CV(& ASSOCS),CKLST PT9a /003-074-018 DP3-74 SUBM 2/21/84; CV FOR 4 ASSOCS SCHADE,STANLEY G ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
		(b) CV-ASSOC(s) # /PT 9b 1 ASST TO TRUMP(#128,3-48-23,3/27/84); DP3-48 SUBM 2/14/83			
L Sep-06-84		AMENDMENT	84-48	DJF	831853
		(a) CKLST PT9a /003-069-002 DP 3-69 SUBM 8/14/84; CV(& ASSOCS) SUBM 5/22/84 & 8/30/83 BERNARD,STEPHEN A CA-LUNG WITH CIS-PLATINUM IN ADENO CA OR LARGE CELL CA			
		(b) CV-ASSOC(s) PT9b /003-071-014 BRENNAN,OLSON,ROWE			
		(c) CV-ASSOC(s) PT9c /003-074-007 JADEJA,MAHAJAN			

Led/ FDA	Event Date	Cross Ref Date	Description	Amendment/ Supplement	Contact -----	Resp Due	Event ID
16,332	IND	MITOXANTHONE	CL 232,315 ANTICANCER AGENT				

L Sep-12-84			AMENDMENT	84-49	DJF		831861
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- (a) CV(& ASSOCs),CKLST
PT9 /003-074-019
DP3-74 SUBM 2/21/84
KARP,DANIEL D
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)

L Sep-19-84			AMENDMENT	84-51	DJF		831878
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- (a) CKLST
PT9a /003-071-035
(3-71-35); CV(& ASSOC) SUBM 1/20/84; DP3-71 SUBM
2/21/84
GEORGE,SEBASTIAN
LYMPHOMA; vs m-BACOD
m-BACOD COMBO
- (b) CV-ASSOC(s) # /PT 9b
2 ASSOCs OF DR BITRAN(#87,3-40-23-10/7/82);3-40
SUBM 7/13/82
- (c) CV-ASSOC(s) # /PT 9c
7 ASSOCs OF PORTLOCK(#156,3-48-29-7/12/84);3-48
SUBM 2/14/83
- (d) DRUG EXPER RPT # /PT 10
PT#1006,3-74-2: DEATH -3hrs AFTER MITO + Ara-C
ADMINISTERED

L Sep-20-84			AMENDMENT	84-52	DJF		831881
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- (a) CV-ASSOC(s) # /PT 9
4 ASSOCs TO TRUMP(#128,3-48-23 3/27/84); DP3-48
SUBM 2/14/83

L Sep-26-84			AMENDMENT	84-53	DJF		850125
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- (a) CKLST,CV-ASSOC(s)
PT9a,b /003-040-021
REPL GOLOMB(#79) AS PR INV IN 3-40 SUBM
7/13/82,AMND 1/10/83
BITRAN,JACOB /GOLOMB
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
GOLOMB,HARVEY M
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp Event ----- Due ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT		

- (b) CKLST, CV-ASSOC(s)
PT9a,b /003-048-010
BITRAN REPL GOLOMB AS PR INV IN 3-48 SUBM 2/14/83,
A 2/28/84
BITRAN, JACOB /GOLOMB
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
BITRAN, JACOB /GOLOMB
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
GOLOMB, HARVEY M
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
- (c) CV-ASSOC(s)
PT9b /003-046-007
3-46 SUBM 12/8/82, AMND 6/21/83; BITRAN'S CV SUBM
10/7/82
- (d) CV-ASSOC(s)
PT9c /003-071-034
FOR 12 ASSTs TO DR M DOSIK (#159-8/16/84); 3-71
SUBM 2/21/84
- (e) PROTOCOL AMENDMENT
PT10a /003-065-000
A#2 -PROT ORIG SUBM 7/29/83, AMND 3/26/83
- (f) PROTOCOL AMENDMENT
PT10b /003-074-000
A#1 -PROT SUBM 2/21/84

L Oct-04-84	AMENDMENT	84-54	DJF	831938
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- (a) CV(& ASSOCs), CKLST
PT9a /003-074-020
3-74 SUBM 2/21/84, AMENDED 9/26/84
WEAVER, ZEBULON III
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)

L Oct-17-84	AMENDMENT	84-55	DJF	831935
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- (a) CV-ASSOC(s)
PT9 /003-071-001
1 ASST TO CASE (#98, 3-71-1 SUBM 2/21/84)

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact -----	Resp Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT				
L Oct-19-84		AMENDMENT	84-56	DJF		831939
		(a) CV-ASSOC(s) # /PT 9 4 ASSTS TO ARLIN (#85,3-44-13,10/1/82); 3-44 SUBM 9/10/82				
L Oct-24-84		AMENDMENT	84-58	DJF		831942
		(a) CKLST & PROTOCOL PT9 /003-074-021 CV SUBM 9/10/82 ARMENTROUT,STEVEN ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)				
L Oct-24-84		CORRESPONDENCE	84-57	DJF		831941
		COPY OF 9/25 MINUTES: EVAL'N OF MITO IN PTS W/ LEUK/LYMPHOMA				
L Oct-29-84		AMENDMENT	84-59	DJF		831962
		(a) CKLST & PROTOCOL PT9,10 /003-000-000 CV SUBM 12/3/82 BERNHARDT,BERNARD				
L Nov-05-84		AMENDMENT	84-60	DJF		832033
		(a) CV-ASSOC(s) PT9 /003-046-002 7 ASSTS TO PETERSON (#94-12/8/82); PROT SUBM 12/8/82				
L Nov-07-84		AMENDMENT	84-61	DJF		832036
		(a) CV-ASSOC(s) PT9a /003-071-013 2 ASSTS TO HOLROYDE(#134-4/16/84); DP3-71 SUBM 2/21/84				
		(b) CV-ASSOC(s) PT9b /003-000-000 PHILLIPS ASST'd BERNHARDT IN PROT SUBM 10/29/84,1PT-COMPASSN				

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
L Nov-09-84	L Oct-24-84	CORRESPONDENCE	84-62	DJF	832038
		(a) PUBLISHED RPTS SWOG PAPER (CANCER '79): ADRIAMYCIN'S CONTRIBUTION DIFF LYMPH			
L Nov-13-84		AMENDMENT	84-63	DJF	832040
		(a) CKLST PT9 /003-069-003 DP3-69 SUBM 8/14/84; CV(& ASSOCS) SUBM 4/9/84, 7/13/82 SARG, MICHAEL J CA-LUNG WITH CIS-PLATINUM IN ADENO CA OR LARGE CELL CA			
L Nov-14-84		AMENDMENT	84-64	DJF	832042
		(a) CV-ASSOC(s) PT9a /003-048-020 ASST TO BERNARD(#117-2/1/84); DP3-48 SUBM 2/14/83, A-2/28/84			
		(b) CV-ASSOC(s) PT9b /003-074-015 2 ASSTs TO DOSIK(#163-8/24/84); DP3-74 SUBM 2/21/84, A9/26/84			
L Nov-27-84		AMENDMENT	84-65	DJF	832067
		(a) PROTOCOL AMENDMENT PT10 /003-046-000 AMNDMT 2 (DP3-46 ORIG SUBM 12/8/82, FIRST AMND 6/21/83)			
L Nov-30-84		AMENDMENT	84-67	DJF	832069
		(a) CV, CKLST PT9 /003-000-000 SPAULDING FOLLOWING (BUT NOT PART OF) DP3-40 SUBM 7/13/82 SPAULDING, MONICA B			
L Dec-05-84		AMENDMENT	84-68	DJF	832103
		(a) CV-ASSOC(s) PT9 /003-071-031 ASST TO WHITE (#116, 7/12/84); DP3-71 SUBM 2/21/84			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

L Dec-20-84 AMENDMENT 84-69 GRP F 832144
IN SUPPORT OF PRESERV EFFICACY -VIALS AS MULT-DOSE
CONTAINER

- (a) PRESERVATIVE EFFICACY # /PT 5
AT 30 MINS; 1,7,14,21,28 DAYS (EXHIBIT #1)
- (b) PRESERVATIVE EFFICACY # /PT 5
AT 6,24,48 HRS & 7,14,21,28 DAYS (EXHIBIT #2)
- (c) ANALYSES # /PT 5
MULT-USE EVAL'N: REPEATED EXTRACTIONS FROM A
SINGLE VIAL 30d
- (d) MONOGRAPH # 15530 /PT 5
GENERAL MTD: ANTIMICROBIAL PRESERVATIVES
EFFECTIVENESS

L Jan-02-85 AMENDMENT 85-1 DJF 932126

- (a) DRUG EXPER RPT
PT10 /003-074-007
PT#2019 DEATH: FIBRILLATION ATRIAL

L Jan-18-85 AMENDMENT 85-2 DJF 850033

- (a) CKLST, PROT
PT9a,10a /003-076-001
CV SUBM 10/4/84
WEAVER,ZEBULON III
CA-SOLID; COMPASSIONATE
- (b) CV,CKLST,PROTO
PT9b,10b /003-077-001
COOPER,MILES R
LEUKEMIA; COMPASSIONATE

F Jan-22-85 L Oct-24-84 CORRESPONDENCE DJF 950274
IF MITO ADDS TO RESULTS OF H-D CYTARAB (ANLL)
EFFICACY SHOWN

- (a) EFFICACY(NOD LYMPH): IMPROVE QUALITY OF
LIFE;SURVIV DATA REQ

L Feb-19-85 AMENDMENT 85-3 DJF 850120

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

- (a) CKLST
PT9a /003-000-000
DP3-65 SUPM 7/29/83, AMENDED 8/26/83, 9/26/84. CV
SUB 2/14/83
HOLLAND, JAMES
- (b) CV, CKLST
PT9b /003-076-002
DP3-76 SUBM 1/18/85
GRILLO, JAMES
CA-SOLID; COMPASSIONATE
- (c) PROTOCOL AMENDMENT
PT10 /003-075-001
A#1: PTS OVER 70yrs WILL BE ADMITTED; DP3-75 SUBM
2/22/84

L Feb-26-85

AMENDMENT 85-4 DJF 850142

- (a) CV-ASSOC(s)
PT9 /003-071-015
ASST TO SHAW (#138 -5/4/84); DP3-71 SUBM 2/21/84
- (b) DRUG EXPERIENCE RPT # /PT 10
(U.K. STUDY 3-563-1, PT# 1/G.N.) INTESTINAL
PERFORATION

L Mar-01-85

AMENDMENT 85-6 DJF 850189

- (a) CV, CKLST
PT9a /003-076-003
PROT SUBM 1/18/85
LOWENBRAUN, STANLEY
CA-SOLID; COMPASSIONATE
- (b) CV(& ASSOCS), CKLST
PT9b /003-076-004
PROT SUBM 1/18/85
SCHER, NANCY
CA-SOLID; COMPASSIONATE
- (c) CKLST
PT10c /003-076-005
PROT SUBM 1/18/85; CV SUBM 7/26/84 UNDER PROT
3-71-32
JAFFREY, IRA S
CA-SOLID; COMPASSIONATE

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(d) CKLST PT10J /003-076-006 PROT SUBM 1/18/85; CV SUBM 3/27/84 UNDER PROT 3-48-5 DENEFRID, JOHN M CA-SOLID; COMPASSIONATE			
		(e) /003-076-0 DR Z WEAVER(#166) WILL BE TREATING AN ADDL PATIENT			
		(f) /003-077-0 DR COOPER(#170) WILL BE TREATING AN ADDL PATIENT			
L Mar-08-85		AMENDMENT	85-8	DJF	850179
		(a) DRUG EXPERIENCE RPT # /PT 10 (CANADA) EXTRAVASATION; SWELLING, BLISTERING, WEAKNESS -HAND			
L Mar-15-85		AMENDMENT	85-8	DJF	850214
		(a) CV(& ASSOCS),CKLST PT9 /003-077-002 PROT SUBM 1/18/85 McFARLAND, JAMES A LEUKEMIA; COMPASSIONATE			
L Mar-25-85		AMENDMENT	85-9	DJF	850239
		(a) CV(& ASSOCS),CKLST PT9a /003-076-007 PROT SUBM 1/18/85 HORVATH, WILLIAM L CA-SOLID; COMPASSIONATE			
		(b) CV-ASSOC(s) PT9b /003-074-015 2 ASSTS TO DOSIK; PROT SUBM 2/21/84			
L Apr-10-85		AMENDMENT	85-10	DJF	850310
		(a) CV,CKLST PT9 /003-076-008 PROT SUBM 1/18/85 STRUM, STEPHEN B CA-SOLID; COMPASSIONATE			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

L Apr-15-85		AMENDMENT	85-11	DJF	850313
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- (a) CKLST,PROT,CV-ASSOC(s)
PT9 /003-074-022
PROT SUBM 2/21/84, AMND 9/26/84; CV SUBM 8/14/84
MOORE,JOSEPH D
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
- (b) DRUG EXPERIENCE RPT
PT10 /003-070-001
PT #25: TISSUE NECROSIS

L Apr-23-85		AMENDMENT	85-12	DJF	850348
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- (a) CV(& ASSOCS),CKLST
PT9 /003-076-009
PROT SUBM 1/18/85
GOTTLEIB,ROBERT J
CA-SOLID; COMPASSIONATE
- (b) /003-071-0
BERKOWITZ (CV SUBM 8/24/84) ADDED AS ASST
INVESTIGATOR

L May-10-85		AMENDMENT	85-13	DJF	850459
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- (a) CV,CKLST
PT9 /003-076-010
PROT SUBM 1/18/85
ROBERTS,JOHN
CA-SOLID; COMPASSIONATE
- (b) CV(& ASSOCS),CKLST,PROT
PT9,10 /003-079-001
SRIDHAR,KASI
CA-HEAD & NECK
- (c) CV(& ASSOCS),CKLST,PROT
PT9,10 /003-080-001
KELSEN,DAVID
CA-STOMACH

L May-14-85		AMENDMENT	85-14	DJF	850458
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Led/ Event FLA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315	ANTICANCER AGENT		

(a) CV,CKLST
PT9a /003-076-011
PROT SUBM 1/18/85
KOO,VICTOR S
CA-SOLID; COMPASSIONATE

(b) CV(& ASSOCs),CKLST
PT9b /003-077-004
PROT SUBM 1/18/85
FORTE,FRANCIS A
LEUKEMIA; COMPASSIONATE

L May-15-85 AMENDMENT 85-15 DJF 850469

(a) CV(& ASSOCs),CKLST
PT9 /003-077-003
PROT SUBM 1/18/85
ALBALA,MAURICE
LEUKEMIA; COMPASSIONATE

L May-21-85 AMENDMENT 85-16 DJF 850473

(a) CKLST
PT9 /003-076-012
PROT SUBM 1/18/85; CV(& ASSOCs) SUBM 5/14/85
FORTE,FRANCIS A
CA-SOLID; COMPASSIONATE

L May-24-85 AMENDMENT 85-17 DJF 850440

(a) CKLST # /PT 9
CURRENTLY ACTIVE INVESTIGATORS (AS OF 4/15/85)
(b) PROGRESS RPT # /PT 10
ABRAMSON,NEIL
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
ALBERTS,DAVID S
CA-OV,COLON; DOSE RANGING
PK OF IP ADMINISTRATION
ALLEGRA/WOODCOCK
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
AMARE
LEUKEMIA

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

ARLIN,ZALMEN A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
ARLIN,ZALMEN A
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
ARLIN,ZALMEN A
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
ARLIN,ZALMEN A
CA-BREAST; SPECIAL-PK
INFLUENCE OF HEPATIC FUNCTION
ARLIN,ZALMEN A
LEUKEMIA

ARLIN,ZALMEN A
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
ARMENTROUT,STEVEN
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
ARMENTROUT,STEVEN
LEUKEMIA

ARMENTROUT,STEVEN
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
BENIGNO,BENEDICT R
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
BENNETT,J/QAZI,RAMAN
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
BENNETT,J/QAZI,RAMAN
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
BERNARD,STEPHEN A
CA-LUNG
WITH CIS-PLATINUM IN ADENO CA OR LARGE CELL CA
BERNARD,STEPHEN A
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
BERNARD,STEPHEN A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

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BERNHARDT, BERNARD
BITRAN, JACOB / GOLOMB
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
BLOCK
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
BLUMING, AVRUM Z
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
BRODORSKY
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
BROWN, GORONWY O
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
BROWN, GORONWY O
LEUKEMIA

BYRNE
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
CASE, DELVYN C
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
CASE, DELVYN C
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
CASE, DELVYN C
LYMPHOMA
NON-HODGKIN'S
CASSILETH
LEUKEMIA

CHLEBOWSKI
CA-BREAST; SPECIAL-PK
INFLUENCE OF HEPATIC FUNCTION
CHLEBOWSKI
HEPATOMA

COHEN, RICHARD J
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
CONRAD, MARCEL E
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

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CONRAD, MARCEL E
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
COOPER, MILES R
LEUKEMIA; COMPASSIONATE

COSTANZI, JOHN J
LYMPHOMA
NON-HODGKIN'S
DAO
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
DENEFRIO, JOHN M
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
DENEFRIO, JOHN M
CA-SOLID; COMPASSIONATE

DESAI
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
DESSER, R K
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
DOROSHON
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
DOSIK, HARVEY
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
DOSIK, MICHAEL H
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
DOTY, GORDON L
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
DOTY, GORDON L
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
DOTY, GORDON L
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
DRESDNER, DAVID M
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)

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DRESDNER, DAVID M
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
DUGAN
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
ERSLEV, ALLAN J
LEUKEMIA

ERSLEV, ALLAN J
LYMPHOMA
NON-HODGKIN'S
PASS, LEROY
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
GABRIEL, DON A
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
GABRIEL, DON A
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
GAMS, RICHARD A
LYMPHOMA
NON-HODGKIN'S
GAMS, RICHARD A
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
GAMS, RICHARD A
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
GAMS, RICHARD A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
GAMS, RICHARD A
LEUKEMIA

GEORGE, SEBASTIAN
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
GEORGE, SEBASTIAN
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
GOLOMB, HARVEY M
LYMPHOMA
NON-HODGKIN'S

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GOODMAN,GARY E
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
GRACE,WILLIAM R
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
GRACE,WILLIAM R
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
GRILLO,JAMES
CA-SOLID; COMPASSIONATE

GROPPE,CARL W
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
HEIM,WILLIAM J
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
HENDERSON,I CRAIG
CA-BREAST; SPECIAL-PK
INFLUENCE OF HEPATIC FUNCTION
HESKETH,PAUL
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
HICKS,WILLIAM J
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
HOLLAND,JAMES
LEUKEMIA

HOLLAND,JAMES F
HOLLAND,JAMES F
ALL
COMBINED w/ VINCRISTINE & DEXAMETHASONE
HOLLAND,JAMES F
LYMPHOMA
COMBINED w/ VINCRISTINE & DEXAMETHASONE
HOLROYDE,CRISTPHER P
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
HORVATH,WILLIAM L
CA-SOLID; COMPASSIONATE

JAFFEY,IRA S
CA-SOLID; COMPASSIONATE

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JAFFREY,IRA S
 LYMPHOMA; vs m-BACOD
 m-BNCOD COMBO
 JONES,ROY
 CA-BREAST; DOSE RANGING
 ESCALATING DOSE -CARDIAC MEASUREMENTS
 JONES,STEPHEN E
 LYMPHOMA
 NON-HODGKIN'S
 KARP,DANIEL D
 ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
 IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
 KENNEDY,PETER S
 LYMPHOMA; vs m-BACOD
 m-BNCOD COMBO
 KLOSS,ROBERT A
 ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
 IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
 KRAKOFF,I H
 KRAKOFF,I H
 CA-BREAST
 COMB w/ CYCLOPHOS, 5-FU X-OVER TO
 ADRIAMYCIN/VINBLASTINE
 KREMENTZ,EDWARD T
 CA-BREAST; vs ADRIAMYCIN
 MULTI-CTR 2nd LINE PTS
 KREMENTZ,EDWARD T
 CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
 CYCLOPHOSPHAMIDE-N-5FU vs
 CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
 LAWSON
 CA-BREAST; vs ADRIAMYCIN
 MULTI-CTR 2nd LINE PTS
 LEVICK
 CA-BREAST; vs ADRIAMYCIN
 MULTI-CTR 2nd LINE PTS
 LEVINE,JAMES D
 LYMPHOMA; vs m-BACOD
 m-BNCOD COMBO
 LOWENBRAUN,STANLEY
 CA-SOLID; COMPASSIONATE

 MABRY,R JAMES
 LYMPHOMA; vs m-BACOD
 m-BNCOD COMBO
 MOORE,JOSEPH O
 CA-BREAST; vs ADRIAMYCIN
 MULTI-CTR 2nd LINE PTS

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MOORE,JOSEPH O
CA-LUNG
WITH CIS-PLATINUM IN ADENO CA OR LARGE CELL CA
MOORE,JOSEPH O
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
MOORE,JOSEPH O
LEUKEMIA

MORGAN,LEE ROY
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
MUGGIA,FRANCO
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
MUSS
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
McFARLAND,JAMES A
LEUKEMIA; COMPASSIONATE

OISHI,NOBORU
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
PETERSEN
LYMPHOMA
NON-HODGKIN'S
PLOTKIN,DAVID
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
PORTLOCK,CAROL S
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
PRESANT,CARY A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
QAZI,RAHMAN
RIVKIN,SAUL E
LYMPHOMA
NON-HODGKIN'S

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ROACH,RALPH W
ROBINSON,WILLIAM
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
POSS
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
SAMUELS,ARTHUR J
SARG,MICHAEL J
CA-LUNG
WITH CIS-PLATINUM IN ADENO CA OR LARGE CELL CA
SARTIANO,GEORGE P
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
SARTIANO,GEORGE P
LEUKEMIA

SCHADE,STANLEY G
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
SCHER,NANCY
CA-SOLID; COMPASSIONATE

SCHWARTZ,I ROBERT
LEUKEMIA

SCOTT,ROBERT B
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
SEBASTIAN,GEORGE
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
SHAW,JOHN
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
SILVER,RICHARD T
LYMPHOMA
NON-HODGKIN'S
SILVER,RICHARD T
LEUKEMIA

SILVER,RICHARD T
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
SILVER,RICHARD T
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

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SPAULDING, MONICA B
SPICER
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
STEIN, RICHARD S
LYMPHOMA
NON-HODGKIN'S
STEIN, RICHARD S
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
STONE, LAWRENCE A
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
STRUM, STEPHEN B
CA-SOLID; COMPASSIONATE

STUART, JOHN J
LYMPHOMA
NON-HODGKIN'S
STUART, JOHN J
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
TRANUM, BILL L
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
TRUMP, DONALD L
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
VILLA, LUIS
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
VOGEL, CHARLES L
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
VOLBERDING
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
VOYCE, GARY F
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WACHI, DENNIS H
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WEAVER, ZEBULON III
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)

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WEAVER,ZEBULON III
CA-SOLID; COMPASSIONATE

WEIDEN
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WEINTRAUB,LEWIS R
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
WHITE

CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
WHITE,CHARLES F
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WHITE,CHARLES F
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WIERNIK,PETER H
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WIERNIK,PETER H
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
WIERNIK,PETER H
LEUKEMIA

WOLFF,STEVEN N
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
WOLFF,STEVEN N
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WOLFF,STEVEN N
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WOODCOCK,THOMAS M
CA-BREAST; SPECIAL-PK
INFLUENCE OF HEPATIC FUNCTION
WOODCOCK,THOMAS M
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO

(c) TOXICOLOGY STUDIES # /PT 10
APPENDED CARDIOTOXICITY REPORT

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16,332	IND	MITOXANTHONE CL 232,315 ANTICANCER AGENT			
L May-29-85		AMENDMENT	85-18	DJF	850512
		(a) CV(& ASSOCs),CKLST PT9a /003-076-014 COMPASSIONATE PROT (SOLID TUMORS) SUBM 1/18/85 NELSON,ERIC C CA-SOLID; COMPASSIONATE			
		(b) CV(& ASSOCs),CKLST PT9b /003-077-005 COMPASSIONATE PROT (LEUKEMIA) SUBM 1/18/85			
L May-30-85		AMENDMENT	85-19	DJF	850511
		(a) CV-ASSOC(s) PT9 /003-074-015 CV FOR DR S ROTHENBERG; PROT SUBM 2/21/84, AMENDED 9/24/84			
L Jun-03-85		AMENDMENT	85-20	DJF	850533
		(a) CV,CKLST PT9 /003-046-003 MILLER REPLACES JONES AS PRINC INVEST; PROT SUBM 12/8/82 JONES,STEPHEN E LYMPHOMA NON-HODGKIN'S MILLER,THOMAS /JONES LYMPHOMA NON-HODGKIN'S			
L Jun-25-85		AMENDMENT	85-21	DJF	850599
		(a) CV-ASSOC(s) PT9a /003-048-029 7 ASSOCs; PROT SUBM 2/21/84			
		(b) CV,CKLST PT9b /003-076-015 COMPASSIONATE PROT SUBM 1/18/85 ARENA,PAUL CA-SOLID; COMPASSIONATE			
		(c) CV,CKLST PT9b /003-076-017 COMPASSIONATE PROT SUBM 1/18/85			

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BUDD, THOMAS G
CA-SOLID; COMPASSIONATE

(d) CV(& ASSOCs), CKLST
PT9c /003-077-006
COMPASSIONATE PROT SUBM 1/18/85
SAUNDERS, DARRELL F
LEUKEMIA; COMPASSIONATE

(e) CV(& ASSOCs), CKLST
PT9d /003-044-000
(ONE PT) FOLLOWING MITO TRTMT SECT OF LEUK PROT
SUBM 9/10/82
ALGAZY, KENNETH M
LEUKEMIA

L Jun-26-85

AMENDMENT 85-22 DJF 850606

(a) CV(& ASSOCs), CKLST, PROT
PT9,10 /003-079-002
ERVIN, THOMAS
CA-HEAD & NECK

L Jul-08-85

AMENDMENT 85-23 DJF 850659

(a) CV(& ASSOCs), CKLST
PT9 /003-080-002
PROT SUBM 5/10/85
BENEDETTO, PASQUALE
CA-STOMACH

L Jul-31-85

AMENDMENT 85-24 DJF 850700

(a) CV-ASSOC(s)
PT9 /003-079-002
2 ASSOCs TO ERVIN (#187); PROT SUBM 6/26/85
(b) PROTOCOL AMENDMENT
PT10 /003-072-000
A#1: OPTIONAL TESTS; PROT SUBM 12/13/83
(c) PROTOCOL AMENDMENT
PT10 /003-072-000
A#2: MISCELLANEOUS CHANGES; PROT SUBM 12/13/83

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16,332	IND	MITOXANTHONE	CL 232,315	ANTICANCER AGENT	
L Aug-02-85		AMENDMENT	85-25	DJF	850769
		(a) CV(& ASSOCs),CKLST PT9ab /003-072-005 UPDATED CVs (PROT SUBM 12/13/83, AMENDED I&II 7/31/85) CASE,DELVYN C CA-BREAST; SPECIAL-PK INFLUENCE OF HEPATIC FUNCTION			
L Aug-06-85		AMENDMENT	85-26	DJF	850753
		(a) PROTOCOL AMENDMENT PT10a /003-046-010 A #2A: MUGA SCAN OR ECHO ALLOWED (PROT SUBM 12/8/82)			
		(b) PROTOCOL AMENDMENT PT10b /003-071-030 A #1A: MUGA SCAN OR ECHO ALLOWED (PROT SUBM 2/21/84)			
L Aug-07-85		AMENDMENT	85-27	DJF	850755
		(a) PROTOCOL AMENDMENT PT10 /003-074-000 A#2: NO CNS LEUK AT BASELINE (PROT SUBM 2/21/84)			
L Aug-12-85		AMENDMENT	95-28	DJF	850791
		(a) CV,CKLST PT9 /003-076-019 PROT SUBM 1/18/85 SMITH,FREDERICK P CA-SOLID; COMPASSIONATE			
L Aug-16-85		AMENDMENT	85-29	DJF	850803
		(a) CV,CKLST PT9 /003-076-022 UPDATED CV; PROT SUBM 1/18/85 BERTINO,JOSEPH CA-SOLID; COMPASSIONATE			

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16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

L Aug-21-85		AMENDMENT	85-30	DJF	850811
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- (a) CV(& ASSOCs),CKLST
PT9a /003-076-023
PROT SUBM 1/18/85
VERDIRAME,JOSEPH
CA-SOLID; COMPASSIONATE
- (b) CV-ASSOC(s)
PT9b /003-079-001
4 ASSTs TO SRIDHAR (#178); CV & PROT SUBM 5/10/85
- (c) CV-ASSOC(s)
PT9b /003-080-002
4 ASSTs TO BENEDETTO (#191 CV SUBM 7/8/85);PROT
SUBM 5/10/85

L Sep-03-85		AMENDMENT	85-31	DJF	850865
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- (a) CKLST
PT9a /003-076-020
PROT SUBM 1/18/85; CV(& ASSOCs) SUBM 5/29/85
PAPISH,STEPHEN W
CA-SOLID; COMPASSIONATE
- (b) CV,CKLST
PT9b /003-076-025
PROT SUBM 1/18/85
KUBOTA,THOMAS T
CA-SOLID; COMPASSIONATE

L Sep-05-85		AMENDMENT	85-32	DJF	850866
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- (a) CV,CKLST
PT9 /003-077-007
UPDATED CV; PROT SUPM 1/18/85
STUART,JOHN
LEUKEMIA; COMPASSIONATE

L Sep-06-85		AMENDMENT	85-33	DJF	850760
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- (a) DRUG EXPERIENCE RPT
PT10 /003-070-001
(FOLL UP TO 4/15/85 RPT) PT#25; TISSUE NECROSIS

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(b) DRUG EXPERIENCE RPT # /PT 10 (AUSTRALIA - COMPASSIONATE PT) TISSUE NECROSIS			
L Sep-23-85		AMENDMENT	85-34	DJF	950840
		(a) CV(& ASSOCS),CKLST PT9a /003-077-010 PROT SUBM 1/10/85			
		(b) DRUG EXPERIENCE RPT # /PT 10 (WG) DEATH: OVERDOSE EFFECT; APLASIA BONE MARROW KOWAL-VERN,ARETA LEUKEMIA; COMPASSIONATE			
L Sep-25-85		AMENDMENT	85-35	DJF	850965
		(a) CV,CKLST PT9 /003-076-018 PROT SUBM 1/18/85 SCHELL,FRANK CJ CA-SOLID; COMPASSIONATE			
		(b) PROTOCOL PT10a /003-075-000 FINAL COPY OF PROTOCOL, ORIGINALLY SUBM 2/22/84			
		(c) PROTOCOL AMENDMENT PT10b /003-075-000 A#2: DOSAGE ADJUSTMT; PROT (RE)SUBM 9/25/85, A#1 - 2/19/85			
L Oct-11-85		AMENDMENT	85-36	DJF	850967
		(a) CV,CKLST PT9 /003-077-009 PROT SUBM 1/18/85 DENHAM,CLAUDE A LEUKEMIA; COMPASSIONATE			
L Oct-16-85		AMENDMENT	85-37	DJF	850974
		(a) CV,CKLST PT9a /003-077-011 UPDATED CV; PROT SUBM 1/18/85 ARLIN, ZALMEN A LEUKEMIA; COMPASSIONATE			

Led/ Event FIA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(b) CV-ASSOC(s) PT9b /003-077-007 FOR 9 ASST INVESTIGATORS; PROT SUBM 1/18/85			
L Oct-23-85		AMENDMENT	85-39	DJF	851018
		(a) SUMMARY, PRECLINICAL # /PT 6 ACUTE INTRAVESICULAR & INTRAPERITONEAL STUDIES IN DOGS			
		(b) CV,CKLST,PROTD PT9 /003-082-001 DP3-78 REV'd/RESUBM'd 1/13/86 AS DP3-82; ALBERTS CV 2/22/84 ALBERTS,DAVID S CA-BLADDER; DOSE RANGING INTRAVESIC ADMIN; DP3-78 REV'd & RESUBM'd 1/10/86 AS DP3-82			
L Oct-23-85		AMENDMENT	85-38	DJF	851007
		(a) CV-ASSOC(s) PT9 /003-037-001 FOR LOCKER, TREATING PT #35 WHO MOVED FROM UCLA TO ILLINOIS			
L Oct-25-85		AMENDMENT	85-40	DJF	851035
		(a) INVESTIGATOR BROCHURE # /PT 7 ISSUE DATE 10/15/85			
L Oct-30-85		AMENDMENT	85-41	DJF	850969
		(a) CV,CKLST PT9a /003-076-033 PROT SUBM 1/18/85 DEUR,CHARLES J CA-SOLID; COMPASSIONATE			
		(b) CV,CKLST PT9b /003-076-026 UPDATED CV; PROT SUBM 1/18/85 MUGGIA,FANCO CA-SOLID; COMPASSIONATE			
		(c) CV,CKLST PT9c /003-076-024 PROT SUBM 1/18/85			

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

WALLACE, JAMES H
CA-SOLID; COMPASSIONATE

(d) CV, CKLST
PT9d /003-077-012
PROT SUBM 1/18/85
DeGREEN, PETER
LEUKEMIA; COMPASSIONATE

(e) CV(& ASSOCs), CKLST
PT9e /003-077-013
PROT SUBM 1/18/85
SCHECTER, CEPALDINE
LEUKEMIA; COMPASSIONATE

(f) DRUG EXPERIENCE RPT
PT10 /003-044-002
PT # 5035 DEATH: JAUNDICE

L Nov-04-85		AMENDMENT	85-42	DJF	851093
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(a) CV(& ASSOCs), CKLST
PT9 /003-046-006
WHEELER REPLACES GAMS AS PRINC INVEST; PROT SUBM
12/8/82
GAMS, RICHARD A
LYMPHOMA
NON-HODGKIN'S
WHEELER, RICHARD
LYMPHOMA
NON-HODGKIN'S

(b) CV(& ASSOCs), CKLST
PT9 /003-044-008
WHEELER REPLACES GAMS AS PRINC INVEST; PROT SUBM
9/10/82
GAMS, RICHARD A
LEUKEMIA

WHEELER, RICHARD
LEUKEMIA

L Nov-11-85		AMENDMENT	85-43	DJF	851101
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(a) CV(& ASSOCs), CKLST
PT9 /003-075-032
COMPASSIONATE PROT SUBM 1/18/85

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

FIELDER, KATHLEEN
CA-SOLID; COMPASSIONATE

L Nov-14-85

AMENDMENT 85-44 DJF 851094

- (a) CV, CKLST
PT9a /003-076-037
COMPASSIONATE PROT SUBM 1/18/85
ROSS, MICHAEL
CA-SOLID; COMPASSIONATE
- (b) CKLST
PT9b /003-048-013
WHEELER (CV SUBM 11/4/85) REPLACES GAMS; PROT SUBM 2/14/83
GAMS, RICHARD A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WHEELER, RICHARD
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
- (c) CKLST
PT9b /003-071-028
WHEELER (CV SUBM 11/4/85) REPLACES GAMS; PROT SUBM 2/21/84
GAMS, RICHARD A
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WHEELER, RICHARD
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
- (d) CKLST
PT9b /003-074-011
WHEELER (CV & ASSOCS' SUBM 11/4/85) REPL GAMS;
PROT 2/21/84
GAMS, RICHARD A
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)
WHEELER, RICHARD
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)

REGULATORY AFFAIRS
DEPT. 956

FOA SUBMISSIONS
SINGLE FOA ID
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16,332	IND	MITOXANTHONE	CL 232,315	ANTICANCER AGENT	
L Nov-18-85		AMENDMENT	85-45	DJF	851104
		(a) CV(& ASSOCs),CKLST PT9a /003-076-034 COMPASSIONATE PROT SUBM 1/18/85 DANNEMAN,Wm G CA-SOLID; COMPASSIONATE			
		(b) CV(& ASSOCs),CKLST PT9b /003-077-014 COMPASSIONATE PROT SUBM 1/18/85 STRAUSS,JAMES F LEUKEMIA; COMPASSIONATE			
F Nov-18-85		REQUIREMENT		DJF	851136
		FDA REQUIRES LED TO SUBMIT PAST PROGRESS REPORTS			
L Nov-21-85		AMENDMENT	85-46	DJF	851116
		(a) CKLST PT9 /003-076-035 CV SUBM 7/9/82; ASSOC CVs SUBM 7/9/82,10/27/83; PROT 1/18/85 LEVICK,STANLEY N CA-SOLID; COMPASSIONATE			
L Nov-26-85	F Nov-18-85	CORRESPONDENCE	85-47	DJF	851137
		LED IS INDEED UP TO DATE IN FILING PROGRESS REPORTS			
L Dec-09-85		AMENDMENT	85-49	DJF	851176
		(a) CV,CKLST PT9 /003-076-028 CV SUBM 3/11/85; PROT SUBM 1/11/85 McFARLAND,JAMES A CA-SOLID; COMPASSIONATE			
		(b) CV,CKLST PT9 /003-076-046 CV SUBM 4/25/84; PROT SUBM 1/11/85			

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

BENNETT, JOHN M.
CA-SOLID; COMPASSIONATE

L Dec-12-85		AMENDMENT	95-50	DJF	951192
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(a) CV,CKLST
PT9 /003-076-044
PROT SUBM 1/11/85
BALA, AYER
CA-SOLID; COMPASSIONATE

(b) CV(& ASSOCS),CKLST
PT9 /003-076-045
PROT SUBM 1/11/85
PANDYA, KISHAN J
CA-SOLID; COMPASSIONATE

L Dec-16-85		AMENDMENT	85-51	DJF	851214
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(a) CV,CKLST
PT9a /003-077-018
PROT SUBM 1/11/85 (UPDATED CV)
SILVER, RICHARD T
LEUKEMIA; COMPASSIONATE

(b) CV,CKLST
PT9b /003-076-051
PROT SUBM 1/11/85
HENDERSON, CHARLES A
CA-SOLID; COMPASSIONATE

L Dec-23-85		AMENDMENT	85-53	DJF	851217
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(a) CV(& ASSOCS),CKLST
PT9 /003-074-025
PROT SUBM 2/21/84
RUBIN, ARNOLD D
ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)
IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)

L Jan-03-86		AMENDMENT	96-1	DJF	960011
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(a) CV # /PT 9
CV FOR DR S SALETAN WHO REPLACES DUKART AS LED
MONITOR

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTHONE	CL 232,315	ANTICANCER AGENT	
		(b) PROTOCOL AMENDMENT			
		PT10	/003-072-000		
		A#3: DELETION OF PK ANALYSES; PROT SUBM 12/13/83			
L Jan-13-86		AMENDMENT	86-1	DJF	860547
		(a) PROTOCOL			
		PT10	/003-082-001		
		PROT REVISED (WAS 3-78) BASED ON TOXICITIES FROM CANADA STUD			
L Jan-15-86		AMENDMENT	86-2	DJF	860548
		(a) CV(& ASSOCS),CKLST			
		PT9	/003-077-015		
		GRONCY,PAULA			
		LEUKEMIA; COMPASSIONATE			
L Jan-17-86		AMENDMENT	86-3	DJF	860549
		(a) CV(& ASSOCS),CKLST			
		PT9	/003-074-026		
		PROT SUBM 2/21/84			
		KATTLOVE,HERMAN			
		ANLL; vs CERUBIDINE & CYTOSAR (ARA-C)			
		IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
L Jan-29-86		AMENDMENT	86-4	DJF	860077
		(a) CV,CKLST			
		PT9a	/003-076-021		
		PROT SUBM 1/11/85			
		PETERSON,JAY T			
		CA-SOLID; COMPASSIONATE			
		(b) CV,CKLST			
		PT9b	/003-077-019		
		PROT SUBM 1/11/85			
		HANSON,JOHN P			
		LEUKEMIA; COMPASSIONATE			
L Feb-03-86		AMENDMENT	86-5	DJF	860092
		(a) CV,CKLST			
		PT9a	/003-076-049		
		PROT SUBM 1/11/85			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		SCHREEDER, MARSHALL T CA-SOLID; COMPASSIONATE			
		(a) CV, CKLST PT9b /003-076-043 PROT SUBM 1/11/85 SCHREEDER, MARSHALL T CA-SOLID; COMPASSIONATE			
L Feb-05-86		AMENDMENT	86-6	DJF	860096
		(a) CKLST PT9 /003-072-006 PROT SUBM 12/3/83; CV(& ASSOCS) SUBM 11/4/85 WHEELER, RICHARD H CA-BREAST; SPECIAL-PK INFLUENCE OF HEPATIC FUNCTION			
L Feb-05-86		AMENDMENT	86-7	DJF	860095
		(a) CV, CKLST PT9a /003-076-050 PROT SUBM 1/11/85 ALAVI, JANE B CA-SOLID; COMPASSIONATE			
		(b) CV, CKLST PT9b /003-076-052 PROT SUBM 1/11/85 BLOW, ALTON J CA-SOLID; COMPASSIONATE			
L Feb-18-86		AMENDMENT	86-8	DJF	860116
		(a) CV(& ASSOCS), CKLST PT9 /003-074-027 PROT SUBM 2/21/84 BICKERS, JOHN M ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
L Feb-19-86		AMENDMENT	86-9	DJF	860102
		(a) CV, CKLST PT9a /003-076-054 PROT SUBM 1/11/85			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		FEINER, ALAN S CA-SOLID; COMPASSIONATE			
		(b) CV, CKLST PT9a /003-076-062 PROT SUBM 1/11/85 FREDRIC, RHETT K CA-SOLID; COMPASSIONATE			
L Feb-25-86		AMENDMENT	86-11	DJF	860148
		(a) CV (& ASSOCS), CKLST PT9 /003-076-048 PROT SUBM 1/1/86 HARRIS, WILLIAM KING, GERALD W CA-SOLID; COMPASSIONATE			
L Feb-25-86		CORRESPONDENCE	86-10	DJF	860159
		FDA AUTH'd TO X-REF IND FOR COOPER, STUART & PACIUCCI'S FILING			
L Mar-19-86		AMENDMENT	86-12	DJF	860215
		LED PROPOSAL FOR EXPEDITING USE OF MITO ON COMPASSION BASIS			
L Mar-19-86		AMENDMENT	86-13	DJF	860216
		(a) CKLST PT9a /003-076-036 GRACE'S CV SUBM 7/13/82; PROT SUBM 1/11/85 GRACE, WILLIAM R CA-SOLID; COMPASSIONATE			
		(b) CV, CKLST PT9b /003-076-040 PROT SUBM 1/11/85 ENGELBERG, CHARLES B CA-SOLID; COMPASSIONATE			
		(c) CV (& ASSOCS), CKLST PT9c /003-077-016 PROT SUBM 1/11/85			

Led/ Event FIA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact -----	Resp Due	Event ID
16,332	IND	MITOXANTHONE CL 232,315 ANTICANCER AGENT				

O'CONNELL, JOSEPH
LEUKEMIA; COMPASSIONATE

L Mar-20-86		AMENDMENT	86-15	DJF		860218
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- (a) CV, CKLST
PT9a /003-077-024
PROT SUBM 1/11/85
SENECAL, FRANCIS M
LEUKEMIA; COMPASSIONATE
- (b) CKLST, CV-ASSOC(s)
PT9b /003-077-026
DESAI'S CV SUBM 11/18/85; PROT SUBM 1/11/85
DESAI, AJIT M
LEUKEMIA; COMPASSIONATE
- (c) CV, CKLST
PT9c /003-077-032
PROT SUBM 1/11/85
MEARS, J GREGORY
LEUKEMIA; COMPASSIONATE

L Mar-20-86		AMENDMENT	86-14	DJF		860217
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- (a) CV(& ASSOCs), CKLST
PT9a /003-076-047
PROT SUBM 1/11/85
GOODWIN, J WENDALL
CA-SOLID; COMPASSIONATE
- (b) CV, CKLST
PT9b /003-076-053
PROT SUBM 1/11/85
STALLINGS, LAWRENCE M
CA-SOLID; COMPASSIONATE
- (c) CV, CKLST
PT9c /003-076-061
PROT SUBM 1/11/85
McMAHON, RICHARD T
CA-SOLID; COMPASSIONATE

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315	ANTICANCER AGENT		
L Mar-21-86		AMENDMENT	86-16	DJF	860219
		(a) CV,CKLST PT9 /003-076-072 PROT SUBM 1/11/85 McKEOWN,JOHN M CA-SOLID; COMPASSIONATE			
L Mar-31-86		AMENDMENT	86-17	DJF	860263
		(a) CV(& ASSOCS),CKLST PT9 /003-072-007 PROT SUBM 12/13/83 BENNETT,JOHN M CA-BREAST; SPECIAL-PK INFLUENCE OF HEPATIC FUNCTION			
		(b) PROTOCOL AMENDMENT PT10 /003-075-001 A#3: ALLOWS FOR CONTINUOUS (UNDRAINED) DWELL TIME			
L Apr-09-86		AMENDMENT	86-18	DJF	860550
		(a) CV(& ASSOCS),CKLST,PROT PT9,10 /003-081-001 HOLLAND,JAMES F CA-BREAST PHS I&II. COMBINATION OF NOVANTRONE W THIOTEPA SMETHOTREXATE			
L Apr-10-86		AMENDMENT	86-19	DJF	860339
		(a) CV(& ASSOCS),CKLST PT9a /003-076-030 PROT SUBM 1/11/85 BEARDEN,JAMES D III CA-SOLID; COMPASSIONATE			
		(b) CV(& ASSOCS),CKLST PT9b /003-076-055 PROT SUBM 1/11/85 NOMANBHROY,YUNUS T CA-SOLID; COMPASSIONATE			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315	ANTICANCER AGENT		
L Apr-15-86		AMENDMENT	86-20	DJF	860341
	(a)	CV,CKLST PT9 /003-076-060 PROT SUBM 1/11/85 HAROLD,SUSAN E CA-SOLID; COMPASSIONATE			
L May-20-86		AMENDMENT	86-21	DJF	860493
	(a)	CV(& ASSOCS),CKLST PT9 /003-074-028 PROT SUBM 2/21/84 STEIN,RICHARD S ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
L May-27-86		AMENDMENT	86-22	DJF	860512
	(a)	CV,CKLST PT9 /003-074-029 PROT SUBM 2/21/84 DARA,PARVEZ ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)			
L Jun-06-86		AMENDMENT	86-23	DJF	860551
	(a)	CV PT9a /003-082-001 UPDATED CV FOR ALBERTS & STANISIC (WHO IS NOW ASSOC INVESTOR)			
	(b)	CV(& ASSOCS),CKLST PT9b /003-082-002 PROT SUBM 1/13/86 SHARIFI,R /LAMB,D CA-BLADDER; DOSE RANGING INTRAVESIC ADMIN; DP3-78 REV'd & RESUBM'd 1/10/86 AS DP3-82			
L Jun-25-86		AMENDMENT	86-23	DJF	860612
	(a)	CKLST # /PT 9 LIST OF CURRENTLY ACTIVE INVESTIGATORS			

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16,332	IND	MITOXANTRONE	CL 232,315	ANTICANCER	AGENT

(b) PROGRESS RPT # /PT 10a
ALSO, REFER TO SAFETY UPDATE SUBM'd 2/25/86 TO NDA
19-297
AHR, DAVID
CA-SOLID; COMPASSIONATE

ALAVI, JANE B
CA-SOLID; COMPASSIONATE

ALBALA, MAURICE
LEUKEMIA; COMPASSIONATE

ALI, I
LEUKEMIA; COMPASSIONATE

ALLEGRA/WOODCOCK
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
AMARE
LEUKEMIA

ARENA, PAUL
CA-SOLID; COMPASSIONATE

ARLIN, ZALMEN A
LEUKEMIA; COMPASSIONATE

ARLIN, ZALMEN A
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
ARMENTROUT, STEVEN
LYMPHOMA; vs m-BACOD
m-BACOD COMBO
ASBURY, ROBERT
CA-SOLID; COMPASSIONATE

BARCOCK, WM
LEUKEMIA; COMPASSIONATE

BALA, AVER
CA-SOLID; COMPASSIONATE

BEARDEN, JAMES D III
CA-SOLID; COMPASSIONATE

BENEDETTO, PASQUALE
CA-STOMACH

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

BENIGNO, BENEDICT R
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
BENJAMIN, ROBERT
CA-SOLID; COMPASSIONATE

BENNETT, JOHN M
CA-SOLID; COMPASSIONATE

BERNARD, STEPHEN A
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
BERNARD, STEPHEN A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
BERTINO, JOSEPH
CA-SOLID; COMPASSIONATE

BIRDWELL, ROBERT
CA-SOLID; COMPASSIONATE

BITRAN, JACOB / GOLOMB
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
BLOCK
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
BLOW, ALTON J
CA-SOLID; COMPASSIONATE

BLUMING, AVRUM Z
LYMPHOMA; vs m-BACOD
m-BACOD COMBO
BRADY, ALBERT
CA-SOLID; COMPASSIONATE

BRODORSKY
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
BUDD, THOMAS G
CA-SOLID; COMPASSIONATE

BURTON, GARY
LEUKEMIA; COMPASSIONATE

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

CASIMIR, MIRTHA
CA-SOLID; COMPASSIONATE

CHLEBOWSKI
HEPATOMA

CHU, ALBERT
LEUKEMIA; COMPASSIONATE

COLEMAN, MORTON
CA-SOLID; COMPASSIONATE

CONRAD, MARCEL E
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
CONRAD, MARCEL E
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
COOPER, MILES R
LEUKEMIA; COMPASSIONATE

COSTANZI, JOHN J
LYMPHOMA
NON-HODGKIN'S
CUSTER, GALEN
LEUKEMIA; COMPASSIONATE

CUTTNER, JANET
LEUKEMIA; COMPASSIONATE

DANNEMAN, Wm G
CA-SOLID; COMPASSIONATE

DAO
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
DARA, PARVEZ
CA-SOLID; COMPASSIONATE

DAVIS, HUGH
CA-SOLID; COMPASSIONATE

DEAN, HERBERT
LEUKEMIA; COMPASSIONATE

Led/ FCA	Event Date	Cross Ref Date	Description	Amendment/ Supplement	Contact -----	Resp Due	Event ID
16,332	IND	MITOXANTRONE	CL 232,315 ANTICANCER AGENT				

DENEFRIO, JOHN M
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
DENEFRIO, JOHN M
CA-SOLID; COMPASSIONATE

DENES, ALEX E
CA-SOLID; COMPASSIONATE

DENHAM, CLAUDE A
LEUKEMIA; COMPASSIONATE

DESAI, AJIT M
LEUKEMIA; COMPASSIONATE

DEUR, CHARLES
LEUKEMIA; COMPASSIONATE

DEUR, CHARLES J
CA-SOLID; COMPASSIONATE

DICKMAN, ELLIOT
CA-SOLID; COMPASSIONATE

DUDOSHIN
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
DOTY, GORDON L
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
DOTY, GORDON L
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
DUGAN
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
DeGREEN, PETER
LEUKEMIA; COMPASSIONATE

ENGELBERG, CHARLES B
CA-SOLID; COMPASSIONATE

ERSLEV, ALLAN J
LEUKEMIA

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FEINER, ALAN S
CA-SOLID; COMPASSIONATE

FIELDER, KATHLEEN
CA-SOLID; COMPASSIONATE

FLETCHER, Wm
CA-SOLID; COMPASSIONATE

FOOTE, SANDRA
CA-SOLID; COMPASSIONATE

FORTE, FRANCIS A
CA-SOLID; COMPASSIONATE

FORTE, FRANCIS A
LEUKEMIA; COMPASSIONATE

FREDRIC, RHETT K
CA-SOLID; COMPASSIONATE

FRIEDMAN, ALLAN
LEUKEMIA; COMPASSIONATE

GEILS, GEORGE
LEUKEMIA; COMPASSIONATE

GEORGE, SEBASTIAN
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
GOCKERMAN, JOHN
LEUKEMIA; COMPASSIONATE

GOODMAN, GARY E
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
GOODWIN, J WENDALL
CA-SOLID; COMPASSIONATE

GOTTLEIB, ROBERT J
CA-SOLID; COMPASSIONATE

GRACE, WILLIAM R
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
GRACE, WILLIAM R
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-M-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

GRACE, WILLIAM R
CA-SOLID; COMPASSIONATE

GRANATIR, ROBERT
LEUKEMIA; COMPASSIONATE

GRONCY, PAULA
LEUKEMIA; COMPASSIONATE

HAN, DIN
LEUKEMIA; COMPASSIONATE

HANSON, JOHN P
LEUKEMIA; COMPASSIONATE

HANSON, JOHN P
CA-SOLID; COMPASSIONATE

HANSON, KARL
CA-SOLID; COMPASSIONATE

HAROLD, SUSAN E
CA-SOLID; COMPASSIONATE

HENDERSON, CHARLES A
CA-SOLID; COMPASSIONATE

HENDERSON, I CRAIG
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS

HESKETH, PAUL
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS

HOLLAND, JAMES F

ALL

COMBINED w/ VINCRISTINE & DEXAMETHASONE

HOUROYDE, CRISTPHER P

LYMPHOMA; vs m-BACOD

m-BACOD COMBO

HORVATH, WILLIAM L

CA-SOLID; COMPASSIONATE

HURD, DAVID

CA-SOLID; COMPASSIONATE

HYMAN, PAUL

CA-SOLID; COMPASSIONATE

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JAFFREY,IRA S
CA-SOLID; COMPASSIONATE

JAFFREY,IRA S
LYMPHOMA; vs m-BACOD
m-BNCOB COMBO
JIM,ROBERT T.S.
LEUKEMIA; COMPASSIONATE

JONES,ROY
CA-BREAST; DOSE RANGING
ESCALATING DOSE -CARDIAC MEASUREMENTS
KAJANI,M
LEUKEMIA; COMPASSIONATE

KAPLAN,BARRY
CA-SOLID; COMPASSIONATE

KELSEN,DAVID
CA-STOMACH

KENNEALEY,GERARD
CA-SOLID; COMPASSIONATE

KING,GERALD W
CA-SOLID; COMPASSIONATE

KOO,VICTOR S
CA-SOLID; COMPASSIONATE

KOWAL-VERN,ARETA
LEUKEMIA; COMPASSIONATE

KRAKOFF,I H
CA-BREAST
COMB w/ CYCLOPHOS, 5-FU X-OVER TO
ADRIAMYCIN/VINBLASTINE
KRAKOFF,I H
KREMENTZ,EDWARD T
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
KUBOTA,THOMAS T
CA-SOLID; COMPASSIONATE

LAWSON
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS

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LEE, EDWARD
LEUKEMIA; COMPASSIONATE

LEVICK
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
LEVICK, STANLEY N
CA-SOLID; COMPASSIONATE

LEVINE, JAMES D
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
LOCKER, GERSHON
CA-SOLID; COMPASSIONATE

LOWENBRAUN, STANLEY
CA-SOLID; COMPASSIONATE

MABRY, R JAMES
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
MEARS, J GREGORY
LEUKEMIA; COMPASSIONATE

MENA, PAUL
CA-SOLID; COMPASSIONATE

MINTON, JOHN
CA-SOLID; COMPASSIONATE

MOORE, ANN
CA-SOLID; COMPASSIONATE

MOORE, JOSEPH
LEUKEMIA; COMPASSIONATE

MOORE, JOSEPH D
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
MORGAN, LEE ROY
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-4-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
MUGGIA, FRANCO
CA-SOLID; COMPASSIONATE

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

MUSS
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
MYERS, ALAN
CA-SOLID; COMPASSIONATE

McFARLAND, JAMES A
LEUKEMIA; COMPASSIONATE

McFARLAND, JAMES A
CA-SOLID; COMPASSIONATE

McKEOWN, JOHN M
CA-SOLID; COMPASSIONATE

McMAHON, RICHARD T
CA-SOLID; COMPASSIONATE

NELSON, ERIC C
CA-SOLID; COMPASSIONATE

NOMANBHOY, YUNUS T
CA-SOLID; COMPASSIONATE

O'CONNELL, JOSEPH
LEUKEMIA; COMPASSIONATE

PANDYA, KISHAN J
CA-SOLID; COMPASSIONATE

PAPISH, STEPHEN W
LEUKEMIA; COMPASSIONATE

PAPISH, STEPHEN W
CA-SOLID; COMPASSIONATE

PARISER, SANFORD
LEUKEMIA; COMPASSIONATE

PAULSON, STEVEN
LEUKEMIA; COMPASSIONATE

PETERSON, JAY T
CA-SOLID; COMPASSIONATE

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PLOTKIN, DAVID
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
PORTLOCK, CAROL S
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
PRESENT, CARY A
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
RIDDICK, DAVID
CA-SOLID; COMPASSIONATE

RIES, CURT
LEUKEMIA; COMPASSIONATE

ROACH, RALPH W
ROBERTS, JOHN
CA-SOLID; COMPASSIONATE

ROEDER, MICHAEL
CA-SOLID; COMPASSIONATE

ROSS
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
ROSS, MICHAEL
CA-SOLID; COMPASSIONATE

ROZEN, SIMON
LEUKEMIA; COMPASSIONATE

RYMER, WM
CA-SOLID; COMPASSIONATE

SARTIANO, GEORGE P
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
SAUNDERS, DARRELL F
LEUKEMIA; COMPASSIONATE

SCHecter, GERALDINE
LEUKEMIA; COMPASSIONATE

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

SCHELL,FRANK CJ
CA-SOLID; COMPASSIONATE

SCHER,NANCY
CA-SOLID; COMPASSIONATE

SCHREEDER,MARSHALL T
CA-SOLID; COMPASSIONATE

SCHWARTZ,JOEL
CA-SOLID; COMPASSIONATE

SEGER,JARELL
CA-SOLID; COMPASSIONATE

SENECAL,FRANCIS M
LEUKEMIA; COMPASSIONATE

SHAW,JOHN
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
SHERMAN,ALFRED I
CA-SOLID; COMPASSIONATE

SHIFMAN,THOMAS
CA-SOLID; COMPASSIONATE

SILVER
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
SILVER,RICHARD T
LEUKEMIA; COMPASSIONATE

SMITH,FREDERICK P
CA-SOLID; COMPASSIONATE

STALLINGS,LAWRENCE M
CA-SOLID; COMPASSIONATE

STASZEWSKI,HARRY
LEUKEMIA; COMPASSIONATE

STEIN,RICHARD S
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO
STONE,LAWRENCE A
LYMPHOMA; vs m-BACOD
m-BNCOD COMBO

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

STRAUSS, JAMES F
LEUKEMIA; COMPASSIONATE

STUART, JOHN
LEUKEMIA; COMPASSIONATE

TALARICO, LILIA
LEUKEMIA; COMPASSIONATE

THOMAS, PAUL
LEUKEMIA; COMPASSIONATE

VERDIRAME, JOSEPH
CA-SOLID; COMPASSIONATE

VINCEGUERRA, VINCENT
LEUKEMIA; COMPASSIONATE

VOGEL, CHARLES
CA-SOLID; COMPASSIONATE

VOGEL, CHARLES L
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
VOLBERDING

CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS

VOYCE, GARY F
LYMPHOMA; vs m-BACOD

m-BACOD COMBO

WACHI, DENNIS H

LYMPHOMA; vs m-BACOD
m-BACOD COMBO

WALLACE, JAMES H
CA-SOLID; COMPASSIONATE

WEAVER, ZEBULON III
CA-SOLID; COMPASSIONATE

WEIDEN
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

WEINBERG, BRUCE
LEUKEMIA; COMPASSIONATE

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WHEELER, R (/GAMS)
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WHEELER, RICHARD
LEUKEMIA

WHITE
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
WHITE, CHARLES F
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WHITE, CHARLES F
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WIERNIK, PETER H
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WILBUR, DAVID
CA-SOLID; COMPASSIONATE

WILLIAMS, THOMAS
CA-SOLID; COMPASSIONATE

WOLF, DAVID
LEUKEMIA; COMPASSIONATE

WOLFF, STEVEN N
CA-BREAST; vs ADRIAMYCIN
MULTI-CTR 2nd LINE PTS
WOLFF, STEVEN N
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WOLFF, STEVEN N
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
WOODCOCK, THOMAS M
LYMPHOMA; vs m-BACOD
m-BNCOO COMBO
WORTMAN, JAMES
CA-SOLID; COMPASSIONATE

ZALUSKY, RALPH
LEUKEMIA; COMPASSIONATE

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		(c) CLINICAL STUDIES PT10b /003-076-000 STATUS OF STUDY DOCUMENTN OF COMPASSION SOLID TUMORS STUDIES			
		(d) CLINICAL STUDIES PT10b /003-077-000 STATUS OF STUDY DOCUMENTN OF COMPASSIONATE LEUKEMIA STUDIES			
L Jul-03-86	T Jul-01-86	CORRESPONDENCE SUMMARY/LISTING OF LOTS USED IN PRESERV-EFF EVALUATION TESTS		GRP	860764
L Jul-15-86		AMENDMENT	86-25	DJF	860668
		(a) INVESTGTR DOCUMENTN AT LEDERLE PT9 /003-076-000 PROT SUBM 1/11/85			
		(b) INVESTGTR DOCUMENTN AT LEDERLE PT9 /003-077-000 PROT SUBM 1/11/85			
L Aug-05-86		AMENDMENT FDA AUTHD TO X-REF OUR IND TO SUPPORT CAPIZZI's IND FILING	86-26	DJF	870744
L Aug-06-86		AMENDMENT	86-25	DJF	870743
		(a) INVESTGTR DOCUMENTN at LEDEPLE PT9 /003-076-000 LIST OF INVESTGTRs RECEIVING DRUG DURING JULY, '86 BROWN,R.S. CA-SOLID; COMPASSIONATE CARDAMONE,JOSEPH CA-SOLID; COMPASSIONATE HOLLISTER,DICKERMAN LEUKEMIA; COMPASSIONATE LEIBOWITC,R CA-SOLID; COMPASSIONATE LINK,JOHN CA-SOLID; COMPASSIONATE			

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

MUCHMORE, ELAINE
CA-SOLID; COMPASSIONATE

MCDONALD, C
CA-SOLID; COMPASSIONATE

(b) INVESTGTR DOCUMENTN PENDING
PT9 /003-077-000
LIST OF INVSTGTRS RECEIVING DRUG DURING JULY, '86
MYSTER, ELAINE
LEUKEMIA; COMPASSIONATE

KOPEL, SAM
LEUKEMIA; COMPASSIONATE

POLMEROV, T.
LEUKEMIA; COMPASSIONATE

RUBIN, ARNOLD
LEUKEMIA; COMPASSIONATE

SCHARFMAN, WILLIAM
LEUKEMIA; COMPASSIONATE

VONHOFF, DANIEL
LEUKEMIA; COMPASSIONATE

F Aug-11-86	L Jul-03-86	REQUIREMENT		GRP	860720
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(a) PRESERVATIVE EFFICACY
LED MUST CLARIFY COMPOSITN/MTD OF MANUF FOR
FORMULNS 24E, 23R

L Aug-14-86		AMENDMENT	86-27	DJF	870742
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(a) CKLST
PT9 /003-048-001
CKLST FOR DR. GREEN WHO IS REPLACING MUGGIA AS
PRINC INVSTGR
GREEN, M
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU
(b) INVESTIGATOR REPLACEMENT
PT9 /003-048-001
MUGGIA REPLACED BY GREEN

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MUGGIA,FRANCO
CA-BREAST; vs ADRIAMYCIN (AS PART OF A COMBO)
CYCLOPHOSPHAMIDE-N-5FU vs
CYCLOPHOSPHAMIDE-ADRIAMYCIN-5FU

L Aug-18-86	F Aug-11-86	CORRESPONDENCE		GRP	860721
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(a) PRESERVATIVE EFFICACY
CLARIFICATION OF COMPOSITION/MANUF'g re PRESERV
EFF EVALUATN

L Sep-02-86		AMENDMENT	86-28	DJF	870702
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(a) INVESTGTR DOCUMENTN at LEDERLE
PT9 /003-076-000
LIST OF INVESTIGATORS RECEIVING DRUG DURING
AUGUST, '86
BERNARD,STEPHEN
CA-SOLID; COMPASSIONATE

BRADY,ALBERT
CA-SOLID; COMPASSIONATE

CHERNOF,DAVID
CA-SOLID; COMPASSIONATE

CHLEBOWSKI,JOAN
CA-SOLID; COMPASSIONATE

FLIPPIN,ANTHONY
LEUKEMIA; COMPASSIONATE

GRUNDBERG,STEVEN
CA-SOLID; COMPASSIONATE

MANUSZAK,PAUL
CA-SOLID; COMPASSIONATE

MILLER,DONALD
CA-SOLID; COMPASSIONATE

OZA,YAGNESH
CA-SOLID; COMPASSIONATE

RENTSCHLER,ROBERT
CA-SOLID; COMPASSIONATE

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

SCHNUR, GARY
CA-SOLID; COMPASSIONATE

WORKMAN, FRANK
CA-SOLID; COMPASSIONATE

(b) INVESTGTR DOCUMENTN PENDING
PT9 /003-077-000
LIST OF INVESTIGATORS REC'd EMERGENCY DRUG SHIPMT
IN AUG. '86
ALLAN, STEVE
LEUKEMIA; COMPASSIONATE

BITRAN, JACOB
LEUKEMIA; COMPASSIONATE

BRASS, LAWRENCE
LEUKEMIA; COMPASSIONATE

KATZ, MARTIN
LEUKEMIA; COMPASSIONATE

KELLERMEYER, ROBERT
LEUKEMIA; COMPASSIONATE

(c) INVESTGTR DOCUMENTN at LEDERLE
PT9 /003-077-000
INVESTIGATOR DOCUMENTN NOW ON FILE (PREVIOUSLY
SHIPPED DRUG)
BURTON, GARY
LEUKEMIA; COMPASSIONATE

MOORE, JOSEPH
LEUKEMIA; COMPASSIONATE

WEINBERG, J
LEUKEMIA; COMPASSIONATE

L Sep-09-86

AMENDMENT 86-29 DJF 860828

(a) CV(8 ASSOCS), CKLST, PROT
PT9a, 10 /003-084-001
CAPIZZI, ROBERT
LEUKEMIA; vs ARA-C, ASPARAGINASE
MITO IN ANLL, ALL, CBL-BL

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16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		(b) CV(& ASSOCs),CKLST,PROT PT9a,10 /003-084-002			
L Oct-01-86		AMENDMENT	86-31	DJF	861028
		(a) CV(& ASSOCs),CKLST PT9 /003-084-003 PROT SUBM 9/9/86 RAAB,STEPHEN LEUKEMIA; vs ARA-C, ASPARAGINASE MITO IN ANLL, ALL, CBL-BL			
L Oct-02-86		AMENDMENT	86-30	DJF	860931
		(a) INVESTGTR DOCUMENTN at LEDERLE PT9 /003-076-115 RECEIVED NOVANTRONE DURING SEPTEMBER, 1986 WDOZNIK,ANTIONETTE CA-SOLID; COMPASSIONATE			
		(b) INVESTGTR DOCUMENTN at LEDERLE PT9 /003-076-116 RECEIVED NOVANTRONE DURING SEPTEMBER, 1986 PUGH,REGINALD CA-SOLID; COMPASSIONATE			
		(c) INVESTGTR DOCUMENTN at LEDERLE PT9 /003-076-117 RECEIVED NOVANTRONE DURING SEPTEMBER, 1986 LEWIN,MARGARET CA-SOLID; COMPASSIONATE			
		(e) INVESTGTR DOCUMENTN at LEDERLE PT9 /003-076-118 RECEIVED NOVANTRONE DURING SEPTEMBER, 1986 KRONER,JOAN CA-SOLID; COMPASSIONATE			
		(f) INVESTGTR DOCUMENTN at LEDERLE PT9 /003-076-119 RECEIVED NOVANTRONE DURING SEPTEMBER, 1986 BOHNEN,ROBERT CA-SOLID; COMPASSIONATE			
		(g) INVESTGTR DOCUMENTN at LEDERLE PT9 /003-076-120 RECEIVED NOVANTRONE DURING SEPTEMBER, 1986			

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16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
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NICHOLS, CRAIG
CA-SOLID; COMPASSIONATE

(h) INVESTGTR DOCUMENTN at LEDERLE
PT9 /003-076-121
RECEIVED NOVANTRONE DURING SEPTEMBER, 1986
PARKER, BARBARA
CA-SOLID; COMPASSIONATE

(i) INVESTGTR DOCUMENTN at LEDERLE
PT9 /003-076-122
RECEIVED NOVANTRONE DURING SEPTEMBER, 1986
BROWER, MARTIN
CA-SOLID; COMPASSIONATE

(j) INVESTGTR DOCUMENTN PENDING
PT9 /003-077-070
REC'D EMERGENCY DRUG SHIPMENTS 9/86; PROPER
DOCUMENTN COMING
BHARDWAHA, SUSHIL
LEUKEMIA; COMPASSIONATE

(k) INVESTGTR DOCUMENTN PENDING
PT9 /003-077-071
REC'D EMERGENCY DRUG SHIPMENTS 9/86; PROPER
DOCUMENTN COMING
BEDROSE, ANTRANIK
LEUKEMIA; COMPASSIONATE

(l) INVESTGTR DOCUMENTN PENDING
PT9 /003-077-072
REC'D EMERGENCY DRUG SHIPMENTS 9/86; PROPER
DOCUMENTN COMING
CASSILETH, PETER
LEUKEMIA; COMPASSIONATE

(m) INVESTGTR DOCUMENTN PENDING
PT9 /003-077-073
REC'D EMERGENCY DRUG SHIPMENTS 9/86; PROPER
DOCUMENTN COMING
OLSON, JOHN
LEUKEMIA; COMPASSIONATE

L Oct-17-86

AMENDMENT

86-15

DJF

860959

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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

- (a) CV
PT9a /003-082-002
CV FOR LAMB, NEW CO-INVESTIGTR TO SHARIFI; PROT
SUBM 1/10/86
SHARIFI R/ LAMB D
CA-BLADDER; DOSE RANGING
INTRAVESIC ADMIN; DP3-78 REV'd & RESUBM'd
1/10/86 AS DP3-82
- (b) CV
PT9b /003-072-002
CV FOR ALI, NEW CO-INVSTGTR TO CHLEBOWSKI; PROT
SUBM 12/3/83
CHLEBOWSKI/ ALI I
CA-BREAST; SPECIAL-PK
INFLUENCE OF HEPATIC FUNCTION
- (c) CV
PT9c /003-046-002
CV FOR MILLER, NEW CO-INVSGTR TO PETERSON; PROT
SUBM 12/9/82
PETERSON / MILLER
LYMPHOMA
NON-HODGKIN'S

L Oct-21-86		CORRESPONDENCE	86-32	DJF	861034
		FDA AUTH'd TO X-REF IND pts. 1-6 TO SUPPORT CHAMPIN'S FILING			

L Oct-24-86		AMENDMENT	86-33	DJF	860969
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- (a) CV(& ASSOCS),CKLST
PT9 /003-084-004
PROT SUBM 9/9/86
TODD,MARY B
LEUKEMIA; vs ARA-C, ASPARAGINASE
MITO IN ANLL, ALL, CBL-BL

L Nov-04-86		AMENDMENT	86-35	DJF	870703
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- (a) INVESTGTR DOCUMENTN at LEDERLE/003-076-0
LIST OF INVESTIGATORS REC'g DRUG DURING OCTOBER
'86
BROOKS,BARRY
CA-SOLID; COMPASSIONATE

BUTLER,FRED O
CA-SOLID; COMPASSIONATE

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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.....
16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

CARPENTER, JOHN
CA-SOLID; COMPASSIONATE

HARWIN, WILLIAM
CA-SOLID; COMPASSIONATE

KISIELIUS, THOMAS
CA-SOLID; COMPASSIONATE

LYSS, ALAN
CA-SOLID; COMPASSIONATE

NEEDLES, BURTON M
CA-SOLID; COMPASSIONATE

RAPHAEL, BRUCE
CA-SOLID; COMPASSIONATE

SPICER, DARCY
CA-SOLID; COMPASSIONATE

(b) INVESTGTR DOCUMENTN PENDING
PT9 /003-077-000
INVESTIGATORS REC'D EMERGENCY DRUG SHIPMENT DURING
OCT. '86
PEMBERTON, CLIFFORD
LEUKEMIA; COMPASSIONATE

PIETRAGALLO, LOUIS
LEUKEMIA; COMPASSIONATE

RAGAB, ABDEL
LEUKEMIA; COMPASSIONATE

SPALDING, MONICA
LEUKEMIA; COMPASSIONATE

(c) INVESTGTR DOCUMENTN at LEDERLE/003-077-0
INVESTIGATOR DOCUMENTN NOW ON FILE (PREVIOUSLY
SHIPPED DRUG)
ALLAN, STEVE
LEUKEMIA; COMPASSIONATE

BRASS, LAWRENCE
LEUKEMIA; COMPASSIONATE

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

SYSTER,ELAINE
LEUKEMIA; COMPASSIONATE

FELBER,NORBERT
LEUKEMIA; COMPASSIONATE

FLIPPIN,ANTHONY
LEUKEMIA; COMPASSIONATE

HOLLISTER,DICKERMAN
LEUKEMIA; COMPASSIONATE

SCHARFMAN,WILLIAM
LEUKEMIA; COMPASSIONATE

VON HOFF,DANIEL
LEUKEMIA; COMPASSIONATE

L Nov-13-86

AMENDMENT 86-37 DJF 870716

- (a) CV(4 ASSOCS),CKLST
PT9 /003-082-003
DP 3-82 SUBM 1/13/86
SAROSDY,MICHAEL
CA-BLADDER; DOSE RANGING
INTRAVESIC ADMIN; DP3-78 REV'd & RESUBM'd
1/10/86 AS DP3-82

L Nov-25-86

AMENDMENT 86-38 DJF 870722

- (a) PHARMACY BROCHURE # /PT 7
UPDATED PHARMACY BROCHURE
- (b) DER NARRATIVE
PT10 /003-075-001
pts# 31-33,35: DEVELOPED INTESTINAL OBSTRUCT
(DOSE-LIM TOX)

L Dec-05-86

AMENDMENT 86-39 DJF 870730

- (a) INVESTGTR DOCUMENTN at LEDERLE
PT9 /003-076-000
RECEIVED EMERGENCY DRUG SHIPMENT DURING
NOVEMBER, '86
BERTOLI,JOSEPH
CA-SOLID; COMPASSIONATE

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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.....
16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

CABANILLAS, FERNANDO
CA-SOLID; COMPASSIONATE

CAMPOS, LUIS
CA-SOLID; COMPASSIONATE

HILL, LAWRENCE
CA-SOLID; COMPASSIONATE

POPOVIC, WILLIAM
CA-SOLID; COMPASSIONATE

SPURR, CHARLES
CA-SOLID; COMPASSIONATE

(b) INVESTGTR DOCUMENTN PENDING
PT9 /003-077-000
RECEIVED EMERGENCY DRUG SHIPMENT DURING NOV. '86
GADUZDA, THOMAS
LEUKEMIA; COMPASSIONATE

HINES, JOHN
LEUKEMIA; COMPASSIONATE

HINES, JOHN
LICHTMAN, STUART
LEUKEMIA; COMPASSIONATE

MAZZA, JOSEPH
LEUKEMIA; COMPASSIONATE

NACHANT, NEIL
LEUKEMIA; COMPASSIONATE

PONE, JACOB
LEUKEMIA; COMPASSIONATE

TISMAN, GLEN
LEUKEMIA; COMPASSIONATE

(c) INVESTGTR DOCUMENTN at LEDEBLE
PT9 /003-077-000
DOCUMENTATION NOW ON FILE (PREVIOUSLY SHIPPED
DRUG)
CAPIZZI, ROBERT
LEUKEMIA; COMPASSIONATE

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE	CL 232,315	ANTICANCER AGENT	

KELLERMEYER, ROBERT
LEUKEMIA; COMPASSIONATE

- (d) DER NARRATIVE
PT10 /003-075-001
11/25/86 DER SHOULD HAVE CITED OVARIAN CANCER AS
INDICATION

1 Jan-20-87

AMENDMENT 87-1 DJF 961315
MONTHLY UPDATE FOR DEC '86 OF COMPASSIONATE USE
3-76,3-77

- (a) INVESTGTR DOCUMENTN at LEDERLE
PT9 /003-076-000
PROTOCOL 3-76 COMPASSIONATE USE / REC'D DEC 86
AJAIKUMAR, B.S.
CA-SOLID; COMPASSIONATE

FURST, ANNETTE
CA-SOLID; COMPASSIONATE

GEERAERTS, LOUIS
CA-SOLID; COMPASSIONATE

LUEDKE, DAN
CA-SOLID; COMPASSIONATE

LUNDBERG W. BRUCE
CA-SOLID; COMPASSIONATE

PATTON, ALLEN
CA-SOLID; COMPASSIONATE

STASZEWSKI, HARRY
CA-SOLID; COMPASSIONATE

TISMAN, GLENN
CA-SOLID; COMPASSIONATE

- (b) INVESTGTR DOCUMENTN PENDING
PT9 /003-077-000
PROTOCOL 3-77 COMPASSIONATE USE
AHMED, FAROUK
LEUKEMIA; COMPASSIONATE

CARTER, PETER
LEUKEMIA; COMPASSIONATE

Led/ Event FIA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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.....
16,332 IND MITOXANTRONE CL 232,315 ANTICANCER AGENT

CRAUT, ERIC
LEUKEMIA; COMPASSIONATE

HYMES, KENNETH
LEUKEMIA; COMPASSIONATE

JHANGANI, HARESH
LEUKEMIA; COMPASSIONATE

KLEIN, LEONARD
LEUKEMIA; COMPASSIONATE

KLEIN, LEONARD
LEUKEMIA; COMPASSIONATE

KNOSPE, WILLIAM
LEUKEMIA; COMPASSIONATE

RICHMOND, CAROL
LEUKEMIA; COMPASSIONATE

STOLBERG, LAWRENCE
LEUKEMIA; COMPASSIONATE

STOLBERG, LAWRENCE
LEUKEMIA; COMPASSIONATE

ZEHNGEHOT, LEE
LEUKEMIA; COMPASSIONATE

(c) INVESTGTR DOCUMENTN at LEDERLE
PT9 /003-077-000
PROTOCOL 3-77 COMPASSIONATE USE / REC'D DEC 86
BITRAN, JACOB
LEUKEMIA; COMPASSIONATE

KATZ, MARTIN
LEUKEMIA; COMPASSIONATE

RUBIN, ARNOLD
LEUKEMIA; COMPASSIONATE

L Feb-04-87

AMENDMENT 87-2 DJF 861301

(a) CV(A ASSOCs),CKLST
PT9 /003-084-005
PROT SUBMITTED 9/9/86

Led/ Event FIA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			

STUART, ROBT
LEUKEMIA; vs ARA-C, ASPARAGINASE
MITO IN ANLL, ALL, CBL-BL

L Feb-25-87

AMENDMENT 97-3 DJF 870083
MTHLY UPDATE FOR JAN '87/COMP. USE PROTS 3-76 /
3-77

- (a) INVESTGTR DOCUMENTN at LEDERLE
/PT 9
PROT 3-76 COMP USE / REC'D JAN '87
- (b) INVESTGTR DOCUMENTN PENDING #
/PT 9
PROT 3-77 COMPASSIONATE USE
- (c) INVESTGTR DOCUMENTN at LEDERLE
/PT 9
PROT 3-77 COMPASSIONATE USE / REC'D JAN '87

L Mar-06-87

AMENDMENT 87-4 DJF 870089

- (a) CV(& ASSOCS),CKLST,PROT
PT9, 10 /003-087-001
PROTOCOL #3-87 CHEMO-HORMONAL IN ADV BREAST CA
ALLEGRA, JOS. C.
CA-BREAST
COMB c TAMOX PREMARIN MTX 5-FU LEUCOVORIN
CA-BREAST
REQUESTED BY DR G.BURKE,MRO
EPREMIAN, BARBARA E
CA-BREAST
COMB c TAMOX PREMARIN MTX 5-FU LEUCOVORIN
CA-BREAST
REQUESTED BY DR G.BURKE,MRO
GENTILE, PATRICK S.
CA-BREAST
COMB c TAMOX PREMARIN MTX 5-FU LEUCOVORIN
CA-BREAST
REQUESTED BY DR G.BURKE,MRO
HAMM, JOHN T.
CA-BREAST
COMB c TAMOX PREMARIN MTX 5-FU LEUCOVORIN
CA-BREAST
REQUESTED BY DR G.BURKE,MRO
SEEGER, JANALL
CA-BREAST
COMB c TAMOX PREMARIN MTX 5-FU LEUCOVORIN
CA-BREAST
REQUESTED BY DR G.BURKE,MRO

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp Even ----- Due ID
16,332	IND	MITOXANTHONE CL 232,315 ANTICANCER AGENT		
		SHETH, SUBHASH P. CA-BREAST COMB c TAMOX PREMARIN MTX 5-FU LEUCOVORIN CA-BREAST REQUESTED BY DR G.BURKE, MRO WOODCOCK, THOS, M. CA-BREAST COMB c TAMOX PREMARIN MTX 5-FU LEUCOVORIN CA-BREAST REQUESTED BY DR G.BURKE, MRO		
L Mar-16-87		CORRESPONDENCE FDA AUTH'D TO X-REF IND FOR PATT'S FILING.	87-5	DJF 870979
		(a) CV PI-YEHUDA PATT PATT, YEHUDA		
L Mar-23-87		AMENDMENT PI- ARNOLD RUBIN	87-6	DJF 870973
		(a) CV(& ASSOCs) PI- ARNOLD RUBIN TREATING-ACUTE NONLYMPHOCTIC LEUKEMIA FERNBACH, BARRY ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE) RUBIN, ARNOLD ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE) YAMUSAH, EMANUEL ANLL; vs CERUBIDINE & CYTOSAR (ARA-C) IN COMBO W CYTOSAR (ARA-C)(CYTARABINE)		
L Apr-01-87		CORRESPONDENCE	87-7	DJF 870645
		(a) PRECLINICAL # /PT 10 NOVANTPONE USED TO TREAT HEPATOCELLULAR CARCINOMA RATAIN, MARK J.		
		(b) COMPONENTS & COMPOSITION # /PT 10 HEPATOCELLULAR CARCINOMA		
		(c) CHEMISTRY # /PT 10		
		(d) MANUF & CONTROLS # /PT 10		
		(e) CLINICAL STUDIES # /PT 10		

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE	CL 232,315	ANTICANCER AGENT	

L May-14-87		AMENDMENT	87-8	DJF	870637
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- (a) PROTOCOL AMENDMENT
PT10 /003-087-001
RADIONUCLIDE SCAN DNE BE4 TREATMENT CYCL WHEN NOV.>
120MG/42

L May-22-87		AMENDMENT	87-9	DJF	870635
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- (a) DRUG EXPERIENCE RPT
PT10 /003-076-149
OVERDOSE OF NOVANTRONE -FEMALE PAT.-COMP.PROT.
BREAST CANCER
- (b) PROTOCOL
PT10 /003-084-000
STUDY WAS STOPPED DUE TO 2 PATIENTS DEATHS
- (c) TRIAL-SITE(S) CLOSED /003-084-0
STUDY 3-84 (ALL SITES 1-5) DISCONTINUED DUE TO
DEATHS
CAPIZZI, ROBERT
LEUKEMIA; vs ARA-C, ASPARAGINASE
MITO IN ANLL, ALL, CBL-BL
HAMPTON, JAMES W
LEUKEMIA; vs ARA-C, ASPARAGINASE
MITO IN ANLL, ALL, CBL-BL
RAAB, STEPHEN
LEUKEMIA; vs ARA-C, ASPARAGINASE
MITO IN ANLL, ALL, CBL-BL
STUART, ROBERT
LEUKEMIA; vs ARA-C, ASPARAGINASE
MITO IN ANLL, ALL, CBL-BL
TODD, MARY B
LEUKEMIA; vs ARA-C, ASPARAGINASE
MITO IN ANLL, ALL, CBL-BL

L May-29-87		AMENDMENT	87-10	DJF	870634
		PI- MAURIE MARKMAN-TREATING OVARIAN CANCER			

- (a) CV # /PT 9
MARKMAN TREATING PAT.W/OVARIAN CANCER USING
INTRAPERITONEAL RT.
MARKMAN, MAURIE
- (a) CV
PI-MAURIE MARKMAN/TREATING OVARIAN
CANCER, INTRAPERITONEAL RT.

led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE CL 232,315 ANTICANCER AGENT			
		MARKMAN, MAURIE			
L Jun-03-87		AMENDMENT	87-11	DJF	870633
		(a) PROTOCOL AMENDMENT			
		PT10 /003-081-001			
		PHASE II-II STDY W/TNM IN PAT.W/ RECURRENT			
		SMETAST.BRST CANC			
L Jun-08-87		AMENDMENT	87-12	DJF	870775
		INV/COMP USE			
		(a) INVESTGTR DOCUMENTN at LEDERLE			
		PT9 /003-076-000			
		INV LIST RECD DRUG FROM FEB-MAY '87 (#s 155 THRU			
		177)			
		BOYLE, EAMONN			
		CA-SOLID; COMPASSIONATE			
		ALLEN, EL			
		CA-SOLID; COMPASSIONATE			
		MACWELL, JOHN			
		CA-SOLID; COMPASSIONATE			
		BRONNE, KENNEDY			
		CA-SOLID; COMPASSIONATE			
		CIMU, PHILIP			
		CA-SOLID; COMPASSIONATE			
		FANGMAN, MICHAEL			
		CA-SOLID; COMPASSIONATE			
		FISHER, JJ			
		CA-SOLID; COMPASSIONATE			
		FORSCHER, CHARLES			
		CA-SOLID; COMPASSIONATE			
		GUY, JERRY T			
		CA-SOLID; COMPASSIONATE			
		HALPERIN, JOSEPH			
		CA-SOLID; COMPASSIONATE			

Led/ Event FDA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
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16,332	IND	MITOXANTRONE	CL 232,315	ANTICANCER AGENT	
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HAYWARD, M
CA-SOLID; COMPASSIONATE

HURTUBISE, MICHEL
CA-SOLID; COMPASSIONATE

JENKINS, JAY
CA-SOLID; COMPASSIONATE

KAYE, STEPHEN
CA-SOLID; COMPASSIONATE

MANDEL, EUGENE
CA-SOLID; COMPASSIONATE

MARILLEY, RALPH
CA-SOLID; COMPASSIONATE

MOYNIHAN, J
CA-SOLID; COMPASSIONATE

PRASTHOFFER, EDW
CA-SOLID; COMPASSIONATE

RYAN, THOMAS
CA-SOLID; COMPASSIONATE

SAWKAR, LAXMIDAS
CA-SOLID; COMPASSIONATE

SLOAN, M
CA-SOLID; COMPASSIONATE

STINE, ANTHONY
CA-SOLID; COMPASSIONATE

L Jun-30-87

ANNUAL REPORT	87-16	DJF	870962
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(a) PROGRESS RPT
86 INV.TREATED 3-76 & 89 TREATED 3-77 SINCE LST
RPT.5/31/86

L Jul-29-87

CORRESPONDENCE	87-15	DJF	870963
FDA AUTH X-REF FOR MARKMAN TO STDY INTRAPERITONEAL			

Led/ Event FIA Date	Cross Ref Date	Description	Amendment/ Supplement	Contact Resp ----- Due	Event ID
16,332	IND	MITOXANTRONE	CL 232,315	ANTICANCER AGENT	

L Aug-03-87		CORRESPONDENCE	87-19	DJF	871010
		DR. JD BITRAN CROSS REF OUR IND/REFRAC METATAST BREAST CA			

L Aug-05-87		AMENDMENT	87-20	DJF	871011
		INV / COMP USE			

(a) INVESTGTR DOCUMENTN at LEDERLE/003-076-0
INV LIST/COMP USE/JUNE & JULY/'S 178-185
BORROW, SAMUEL
CA-SOLID; COMPASSIONATE

EISENBERG, PETER D
CA-SOLID; COMPASSIONATE

GLOWALLA, MICHAEL
CA-SOLID; COMPASSIONATE

KAMPEL, LEWIS
CA-SOLID; COMPASSIONATE

SALTZMAN, MARK
CA-SOLID; COMPASSIONATE

SPITZER, GARY
CA-SOLID; COMPASSIONATE

TIRUMALI, NAGENDRA
CA-SOLID; COMPASSIONATE

YAMAMOTO, KENNETH S
CA-SOLID; COMPASSIONATE

L Aug-07-87		AMENDMENT	87-21	DJF	871004
		PROT AMENDMENT #1 / #3-82			

(a) PROTOCOL AMENDMENT /003-082-0
PROT #3-82 AMEND OUTLINES DOSE ESCALATION FOR NEW PATIENTS

L Aug-12-87		AMENDMENT	87-22	DJF	871009
		PI-4.MARKMAN TREATING 2ND PT/OVARIAN CA/1ST PT 5/29/87			

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DEPT. 956

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			

L May-09-84		MEETING REQUEST MTG 5/22: POSSIBILITY OF MULTIPLE-DOSE CLASSIFICATION		GRP	831426
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L May-18-84		INITIAL SUBMISSION 166 VOLUMES. BREAST INDICATION		DRS	831482
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- (a) TABLE OF CONTENTS
vols 1.1 - 1.26; OPTIONAL EXPANDED SUMMARY
- (b) LABEL # /PT 4
vol 1.26
- (c) COMPONENTS & COMPOSITION # /PT
6,7
vol 1.26
- (d) MANUF & CONTROLS
vol 1.27-8
- (e) PRECLINICAL # /PT 10
vols 1.29 - 1.39; RPT Nos. 1-159
- (f) BIOPHARMACEUTIC PKG
vols 1.40-44
- (g) BIBLIOGRAPHY
vols 1.45-48
- (h) DRUG EXPER RPT
vols 1.49-50
- (i) CLINICAL STUDIES
vols 1.51-2; PHARMACOKINETIC STUDIES
- (j) CLINICAL STUDIES
vols 1.53-77; DOSE TOLERANCE STUDIES
- (k) CLINICAL STUDIES
vol 1.78 - 1.150; CONTROLLED STUDIES
- (l) CLINICAL STUDIES
vols 1.151-155; OTHER CLINICAL STUDIES
- (m) CLINICAL STUDIES
vol 1.156; CLINICAL LAB STUDIES RELATED TO SAFETY
- (n) CLINICAL STUDIES
vols 1.157 - 1.166; SPECIAL PATIENTS

L Oct-24-84		CORRESPONDENCE PATENT & EXCLUSIVITY INFO PER MCGINNIS' REQUEST, 10/23/84		ECM	831985
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L Nov-12-84	L Oct-24-84	CORRESPONDENCE PATENT & EXCLUSIVITY INFO (CORRECTS 10/24/84 COMMUNICATION)		GMM	832039
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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
L Nov-28-84		CORRESPONDENCE	84-66	DJF	832068
		(a) SUMMARY, CLINICAL PROPOSED DRAFT SUMMARY BASIS OF APPROVAL			
L Jan-23-85		CORRESPONDENCE		DJF	850044
		AS REQUESTED BY CSO ALETA SINDELAR			
		(a) PUBLISHED RPTS METASTATIC BREAST CANCER (CANCER CLIN TRIALS 4:355-362, '81)			
L Apr-17-85		MEETING		DJF	850327
		AGENDA FOR 5/2/85 MTG re RESUBMN OF CLIN DATA FOR META BR CA			
L May-28-85	M May-02-85	CORRESPONDENCE		DJF	850508
		REVIEW OF LED's UNDERSTANDING OF THE 3/28 & 5/2/85 MEETINGS			
L Jul-12-85	L May-18-84	NOT APPROVABLE		DJF	850714
		LED MUST SUBMIT AMENDMENT CORRECTING DEFICIENCIES			
L Oct-21-85	F Jul-12-85	AMENDMENT		DJF	851114
		RESUBMISSION FOR BREAST INDICATION (INIT'L SUBM 5/18/84)			
F Nov-20-85	L Oct-21-85	CORRESPONDENCE		DJF	851157
		10/21/85 SUBM CONSIDERED MAJOR AMNDMT -NEW 180 DAY REVIEW PD			
L Nov-20-85	F Jul-12-85	AMENDMENT		DJF	860081
		RESPONSE TO 7/12 DEFIC LTR re MANUF/CTRLS NOT ADDRESSD 10/18			
		(a) LABEL-REVISED DRAFT, CONTAINER # 17312 TEXT CODE: PRD2 10ml VIAL			
		(b) LABEL-REVISED DRAFT, BOX # 17311 TEXT CODE: PRD2 10ml VIAL			

Led/ FDA	Event Date	Cross Ref Date	Description	Amendment/ Supplement	Contact -----	Resp Due	Event ID
19-297	NDA	NOVANTRONE	*MITOXANTRONE INJ				
			(c) LABEL-REVISED DRAFT, CONTAINER # 17313 TEXT CODE: PRD2 15ml VIAL				
			(d) LABEL-REVISED DRAFT, BOX # 17314 TEXT CODE: PRD2 15ml VIAL				
			(e) LABEL-REVISED DRAFT, BOX # 17310 TEXT CODE: PRD2 12.5ml VIAL				
			(f) LABEL-REVISED DRAFT, BOX # 17309 TEXT CODE: PRD2 12.5ml VIAL				
			(g) LABEL-REVISED DRAFT, PKG INSERT # 17303 TEXT CODE: PRD4				
			(h) FORMULATION # /PT 7 COMPOSITION OF BOTH CLIN FORM'S I & II (PROP'D COMM'L FORM)				
			(i) CONTROLS # /PT 8(c) IN-PROCESS CTRLS--GOSPORT PRODUCTION (PER ITEM#2, 7/12 LTR)				
			(j) MONOGRAPH # /PT 8(d) SPECS FOR RAW MATERIAL & COMPONENTS				
			(k) AUTHORIZATION # /PT 8(n) HALDANE & WICKHAM LABS LTRS AUTH'g FDA TO X-REF THEIR DMFs				
			(l) STABILITY # /PT 8(p) SUMMARY & REPORTS				
			(m) ANALYSES REPORT OF ANALYTICAL FINDINGS FOR CL 232,315				
L Dec-06-85		L Oct-21-85	CORRESPONDENCE REPL PAGES (REPRESENTING CORRECTIONS) v2.41 pp 75-77, 87, 89		DJF		851175
L Jan-10-86			AMENDMENT		GRP		860021
			(a) MANUF & CONTROLS HEINRICH MACK NACHF. AMNDMT TO DMF#5203 FOR MANUFg MITO BULK				
L Jan-20-86		L Oct-21-85	CORRESPONDENCE		DJF		860032
			(a) CLINICAL STUDIES REANALYSIS OF DURATION OF RESPONSE DATA (NO SIGNIFICNT DIFF)				

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
L Jan-23-86		CORRESPONDENCE LIST OF INDIVIDUALS PARTICIPATING IN 3/6/86 ONCOL ADVIS MTNG		DJF	860066
L Jan-23-86		CORRESPONDENCE		DJF	860068
		(a) SUMMARY, CLINICAL 20 COPIES FOR ADVISORY COMM REVIEW/MTG 3/6; NOT FILED IN NDA			
F Jan-27-86	L Nov-20-85	CORRESPONDENCE 11/20/85 AMNDMT DEEMED "MAJOR" --ADDL 2mo ADDED TO REVIEW PD		DJF	860074
L Jan-28-86		CORRESPONDENCE		DJF	860067
		(a) CASE REPORT FORM LISTING OF CRF's (AS REQ'd BY TURNER) FROM 10/18/85 SUBM			
L Feb-05-86		TELEPHONE CALL MR. MEYER re FEASABILITY OF CYAN SPONSRSHP OF ADVIS COMM MTG		ECM	870059
F Feb-18-86	L Jan-10-86	CORRESPONDENCE 1/10/86 AMNDMT DEEMED "MAJOR" --REVIEW PD EXT 1 Mo.--7/23/86		GRP	860127
L Feb-25-86	L Oct-21-85	CORRESPONDENCE		DJF	860146
		(a) SAFETY UPDATE - CLINICAL SAFETY UPDATE OF 10/21/85 RESUBMISSION			
L Feb-26-86	T Feb-13-86	CORRESPONDENCE RESPONSE TO BURKE'S ?? re CARDIOTOX RPT - v2.40, 10/21 RESUB		DJF	860152
B Mar-14-86		MEETING ADV COMM MTG (9-2 FAVOR NOVANT "ALTERNATIVE" TO ADRIA IN MBC		ECM	870060

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
L Mar-19-86	M Mar-14-86	CORRESPONDENCE GLOSSIES OF SLIDES USED IN LED PRES'n AT ADVIS COMMITTEE MTG		DJF	860226
L Mar-24-86	M Mar-14-86	CORRESPONDENCE MEMO TO SUTHERLAND: FOLLOW-UP REMARKS OF MTG(APPRVL TIMETBL)		ECM	870061
F May-30-86	L May-18-84	NOT APPROVABLE MANUFg, STABILITY, LABELING, CLINICAL PHARM, PK DEFICIENCIES		DJF	860528
L Jun-09-86	F May-30-86	AMENDMENT RESPONSE TO MANUF'g & CONTROL DEFICIENCIES NOTED IN 5/30 LTR		GRP F	860538
		(a) MANUF & CONTROLS # 15201f(g) /PT 8h			
		(b) FORMULA & SOI # /PT 8b			
		(c) STABILITY REPORT # 86-494 /PT 8n 2mg/ml, UPDATE RPT			
L Jun-10-86	F May-30-86	CORRESPONDENCE AS REQ'd, 4 COPIES OF METHODS VALIDATION PACKAGE		GRP	860537
L Jul-16-86	F May-30-86	CORRESPONDENCE		DJF	860669
		(a) LABEL # 14545 TEXT CODE: PRD5 INSERT PROPOSED BY FDA w/ LEDERLE ALTERNATIVE WORDg/DELET'Ns			
L Aug-04-86		VALIDATION AS PER FDA CHEMIST (DR TOLGYESI) INSTRUCTIONS		GRP	860719

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
		(a) SAMPLES			
		1x5gm SAMPLES (CGBL & WG) & REFERENCE STNDS FOR VALIDATIONS			
L Aug-06-86		VALIDATION		GRP	860756
		SAMPLES/REFERENCES STNDS TO BE USED FOR VALIDATION STUDIES			
F Aug-19-86	L Jul-16-86	CORRESPONDENCE		GRP	860704
		7/16/86 AMNDMT DEEMED "MAJOR"; ADDL 60 DAYS FOR REVIEW PD			
F Sep-08-86	L Jun-10-86	CORRESPONDENCE		DJF	860827
		JUNE 9&10 AMDMTS "MAJOR" --2mo ADDED TO REVIEW PD: 8/10/86			
F Oct-07-86		NOT APPROVABLE		DJF	861059
L Oct-17-86		MEETING		DJF	861033
		LED REQUESTS MTG re FURTHER REQRMTS FOR NDA APPROVAL			
L Nov-24-86	M Dec-18-86	MEETING		DJF	870718
		PROPOSED AGENDA & LIST OF LED ATTENDEES FOR 12/18/86 MEETING			
L Dec-10-86	M Dec-18-86	MEETING	86-40	DJF	870731
		BACKGROUND INFO FOR UPCOMING MTG, 12/18/86			
L Mar-12-87	L Jun-23-27	AMENDMENT		DJF	870982
		DATA TAPES W/FULL RPTS OF REFORMATTED SUMMARY TABLES			
L Mar-12-87	L Dec-18-86	MEETING		DJF	870981
		INTENT TO SUBMIT FULL RE-EVAL.& CLIN.SUMMARYOF 4-52			
		(a) CORRESPONDENCE			
		INTENT TO SUBMT RE-EVAL. & CLIN SUMMARY OF STDY 4-52			

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ				
L Mar-19-87	F May-30-86	AMENDMENT 21 PRECLINICAL RPTS/9VOL INCLUDING FULL SUMMARIES FOR 3 STDS		DJF		870977
		(a) PRECLINICAL REPORT(s) REQUEST FROM FDA-TEL 6/23 & 8/27				
F Apr-23-87	Y Mar-12-87	* TELEPHONE CALL DR G BURKE, MRO		DJF	L	870291
		RE OUR 3/12/87 PROPOSAL FOR UPDATING 4-52, HE REQUESTED UPDATED SURVIVAL & CARDIOTOX DATA ALSO BE SUBMITTED FOR 3-48. THEY MIGHT ALSO BE INTERESTED IN SAME FOR 3-40. WILL CONFIRM IN OFFICIAL LETTER.				
F Apr-27-87	L Mar-19-87	ACKNOWLEDGEMENT SUBM NOT SUFFICIENT-NOT BEING PROCESSED AS AMENDMENT		DJF		870976
L May-05-87		# TELEPHONE CALL DR G BURKE, MRO		DJF		871452
		DR POSNER CALLED DR BURKE RE BREAST CANCER AMENDMENT AND PRE-NDA MTG ON LEUKEMIA. ALSO DISCUSSED THE POSSIBILITY OF A TREATMENT IND.				
F May-08-87	Y Mar-12-87	# TELEPHONE CALL DR KARL LINN, BIOMETRICS		DJF		870491
		HE INDICATED HE WAS HAVING A PROBLEM READING THE CARCINOGENECITY TAPES(SUBMITTED ON 3/12/87) INTO HIS COMPUTER. DR GOLDBERG TO CALL HIM BACK ON THE MATTER.				
F May-14-87		* TELEPHONE CALL DR. CARL LINN, BIOSTAT 5/8/87-TAPES SUBM. 3/12/87		DJF		870502
		REQUESTED INFO RE CARCINOGENECITY TAPES PROVIDED TO FDA ON 3/12/87. DR GOLDBERG PROVIDED CLARIFICATION INCLUDING ADDITIONAL TAPE SPECS.				

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
L May-15-87		CORRESPONDENCE INFO ON EFFECT OF NOV. IN LEUKEMIA IN PREP FOR PRE-NDA MEET		DJF	870636
L May-21-87		# MEETING DR G BURKE, MRO		DJF	871336
		OBTAINED ADVANCED COPY OF FDA LETTER REQUESTING ADDITIONAL DATA ON 3-40 & 3-48.			
F May-28-87		* TELEPHONE CALL MS A SINDELAR,CSO		DJF	870583
		PRE-NDA MTG TO DISCUSS LEUKEMIA FILING ARRANGED FOR JULY 7 AT 1:30PM IN 14B/45 AT FDA. DRS TEMPLE & BOTSTEIN + ONCOLOGY DIVISION STAFF WILL ATTEND.			
L Jun-29-87		MEETING PREP FOR PRE-NDA MTG.7/7/87 - SENT TABLE OF CONTENTS	87-14	DJF	870969
		(a) CORRESPONDENCE SENT TABLE OF CONTENTS FOR LEUKEMIA FILING			
L Jul-07-87		# MEETING DR. TEMPLE AND ONCOLOGY DIVISION MEMBERS		DJF	870789
L Jul-21-87		CORRESPONDENCE MINUTES OF PRE-NDA MTG W/FDA 7/7/87		DJF	871322
L Jul-21-87		* TELEPHONE CALL DR R TEMPLE,DIRECTOR		DJF	871002
		DR CARTWRIGHT SPOKE WITH DR TEMPLE FOLLOWING UP OUR MTG OF 7/7/87. TEMPLE POSITIVE ABOUT THE LEUKEMIA CLAIM AND ANXIOUS TO RECEIVE DATA ON BREAST & LEUKEMIA ASAP AS YHE NEXT ADVISORY MTG IS SCHEDULED FOR EARLY DECEMBER.			

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
L Jul-23-87		MEETING DR D HERSEY, SEC ONCOL ADV COMMITTEE		DJF	870911
		NEXT ADVISORY COMMITTEE TENTATIVELY SCHEDULED FOR DECEMBER 7-8, 1987.			
L Jul-28-87		DRUG EXPERIENCE RPT SAFETY EVENT REPORT-NETHERLANDS #3062	87-17	DJF	870961
		(a) SAFETY UPDATE DEAF & BLIND AFTER TREAMNT-DIED FEW DAYS LATER PAT.#3062			
L Jul-29-87		CORRESPONDENCE LETTER OF AUTHORIZATION FOR SPEITZER	87-18	DJF	870960
		(a) AUTHORIZATION STDYING ETOPOSIDE&THIO.W/AUTOLOGOUS MARROW SUPPT/BREST CANCR			
L Aug-17-87		* AMENDMENT RAW DATA FOR UPDATES ON 4-52, 3-40, & 3-48		DJF	871091
		(a) CASE REPORT FORM FDA REQUESTS:5/30/86;10/6/86;5/10,1987:PROT 4-52,3-40,3-48 RAW DATA SUBMITTED FOR BREAST STUDIES 4-52, 3-40, & 3-48			
L Aug-26-87		TELEPHONE CALL DR D HERSEY, SEC ONCOL DRUGS ADV COMM		DJF	871335
		LATEST LIST OF PANEL MEMBERS FROM ADVISORY PANEL REC'D.MTG TENTATIVELY SCHEDULED FOR 12/7&8.			
L Sep-09-87		CORRESPONDENCE RE-REQUEST FOR GOSPORT INSPECTION AFTER 1ST REQ. CANCELLED		GRP	871391
L Sep-11-87		* TELEPHONE CALL DR J JOHNSON, GR DIRECTOR ONCOLOGY		DJF	871111

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DR JOHNSON RECEPTIVE TO PIECEMEAL SUBMISSION OF
LEUKEMIA CLAIM. WOULD DO HIS BEST TO REVIEW BEFORE
ADVISORY MTG IN DECEMBER.

F Sep-15-87		* TELEPHONE CALL DR G BURKE, MRO		DJF	871117
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REQUESTED CRFS FOR 4-52 RESPONDERS WHOSE RAW DATA
WERE NOT INCLUDED IN 8/87 FILING.

L Sep-16-87		* TELEPHONE CALL DR J JOHNSON, ONCOLOGY GROUP DIRECTOR		DJF	871128
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DISCUSSED SCHEDULE FOR PIECEMEAL FILING OF
LEUKEMIA CLAIM & CONTENT OF PACKAGE FOR ADVISORY
COMMITTEE IN DECEMBER.

L Sep-16-87		CORRESPONDENCE LIST OF SUBMISSIONS FOR NEXT MONTH FOR BREAST & LEUKEMIA		DJF	871230
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L Sep-16-87		CORRESPONDENCE LIST OF RESPONDERS IN THE 4-52 STUDY OF NOV. IN BREAST CANCER		DJF	871229
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(a) CORRESPONDENCE
LIST OF RESPONDERS IN 4-52 STUDY OF NOV. IN BREAST
CANCER.

L Sep-18-87	L Sep-11-87	TELEPHONE CALL		DJF	871199
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NOTIFIED DR. JOHNSON ABOUT PIECEMEAL SUBM. OF COMP
FOR LEUKEMIA & BREAST WHICH WILL HOPEFULLY ALLOW
INCLUSION OF BOTH CLAIMS ON AGENDA FOR ADV. COMM
MTG.

L Sep-21-87		* AMENDMENT CASE RECORDS FOR 3-74 & 3-603 LEUKEMIA TRIALS		DJF	871228
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(a) CLINICAL STUDIES
TREATMENT OF ADLT ACUTE NON-LYMPH LEUKEMIA/OD
GRANTED 7/13/87

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
		CRF'S FOR 3-74 AND 3-603 FILED TO FDA AS PART OF APRECLINICAL SUBMISSION FOR A CLAIM IN ANLL. ADDITIONAL SUBMISSIONS PROJECTED FOR SEPTEMBER 30 AND OCTOBER 15.			
L Sep-22-87		TELEPHONE CALL		DJF	871130
		DR D HERSEY, SEC ONCOL DRUGS ADV COM			
		DR ALBERT BERNARTH ADDED TO ONCOLOGIC DRUGS ADVISORY PANEL. NO OFFICIAL AGENDA ITEMS IDENTIFIED.			
L Sep-30-87	F	* AMENDMENT		DJF	871198
		5/30/86, 10/7/86, 5/20/87, MTGS: 12/18/86 & 7/7/87			
		(a) CORRESPONDENCE			
		RESPONSE TO PHARMACOK. QUESTIONS FROM FDA LETTER 5/30/86			
		(b) SUMMARY, CLINICAL			
		UPDATED 4-52 SUMM./SURV. CURVES 3-40 & 3-48/CLIN. PHARM. SUMM.			
		UPDATE OF 4-52, 3-40 AND 3-48 + RESPONSE TO PK QUESTIONS-REPRESENTS A FULL RESPONSE TO FDA LETTERS 5/30/86, 10/7/86 AND 5/20/87.			
L Oct-01-87		* CORRESPONDENCE		DJF	871161
		DR CARTWRIGHT'S COMMENTS TO DR TEMPLE RE BR & LEUK SUBMISS.			
		DR CARTWRIGHT INFORMS DR TEMPLE VIA LETTER ABOUT OUR PLANS FOR PIECEMEAL FILINGS FOR THE BREAST AND LEUKEMIA CLAIMS.			
L Oct-02-87		* AMENDMENT		DJF	871197
		CLINICAL DATA TO SUPP. ADULT ACUTE NON-LYMPHOCYTIC LEUKEMIA			
		(a) CLINICAL REPORT(s) # /PT b			
		MULTI-CTR STDY 3-74+ARA-CVS. CERUBIDINE+ARA-C/11 SUPP. STUDIES			
		(b) BIBLIOGRAPHY			
		+REPRINTS ITEM#8 REPRES. COMBINED CLIN & STAT PRESENTATION			

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
		NDA AMENDMENT INCLUDING CLINICAL REPORTS OF 3-74 & 11 SUPPORTIVE TRIALS + A CLINICAL BIB SUBMITTED TO FDA.			
L Oct-09-87		# TELEPHONE CALL		DJF	871196
		OCT 8 SPOKE W/DR. HERSEY ABOUT PREP FOR ADVISORY COMM. IN DEC. HE NOTED BOTH LEUK. & BREAST CLAIMS FOR NOV. WERE TENTATIVELY ON AGENDA. LEUK-MORNING OF DEC.7 W/ BREAST IN AFTERNOON. CONTINGENT UPON FDA REVIEWING PKGS. SUBM. & ONES TO BE FILED.HE ADDED THAT CRITERIA FOR APPROV. OF A SOLID TUMOR TYPE (OVARIAN CANCER) MIGHT BE AN AGENDA ITEM.NEEDTO C/B IN A COUPLE WEEKS FOR MORE INFO.			
F Oct-16-87		VALIDATION		GRP	880066
		VALIDATION TESTING COMPLETE & SUITABLE W/MODIFICATIONS			
F Oct-16-87		# VALIDATION		GRP	880036
		METHODS VALIDATION APPROVED WITH SOME MODIFICATIONS			
F Oct-16-87		# TELEPHONE CALL		DJF	871265
		DR G BURKE, MRO			
		SPOKE WITH DR MARCUS RE CASES OF HYPERBILIRUBINEMIA IN 3-74 LEUKEMIC PATIENTS AND CODING/TRANSCRIPTION ERRORS IN DOCUMENTING ADR'S.			
L Oct-19-87		* CORRESPONDENCE		DJF	871321
		PROPOSED LABELNG-REQUESTED BY A.SINDELAR 10/16/87-BREAST			
		PROPOSED BREAST LABELING FORWARDED TO FDA.			
F Oct-20-87		ACKNOWLEDGEMENT		DJF	871418
		BR CA DEFICIENCIES:ITEMS 6 (PHARMACO) & 8 (CLIN & STAT)			

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
L Oct-21-87	L Mar-12-87	CORRESPONDENCE REPLCMNT TAPE-NB8238 RAT CARCINOGEN. STDY #81152		DJF	871320
L Oct-22-87		* CORRESPONDENCE DOCUMENTATION FOR ADVISORY COMM FOR DECEMBER MTC		DJF	871319
		(a) LABEL-DRAFT, PACKAGE INSERT COVERNG USE IN BOTH LEUKEMIA & BREAST CANCER			
		(b) CLINICAL REPORT(S) MULTICENTER STUDIES: 3-603, NOV + ARA-C VS CERUBIDINE+ARA-C			
		FINAL INSTALLMENT OF CLINICAL DATA TO SUPPORT THE LEUKEMIA(ANLL) CLAIM FILED AT FDA. SUBMISSION INCLUDES 3-603 CLINICAL REPORT, INTEGRATED SUMMARIES OF SAFETY & EFFICACY AND PROPOSED LABELING COVERING BOTH THE LEUKEMIA & BREAST CA CLAIMS.			
F Oct-28-87		* TELEPHONE CALL DR G BURKE, MRO		DJF	871328
		PHONED DR S MARCUS REQUESTING INFORMATION ON LEUKEMIA STUDY 3-603 RELATED TO MISSING BONE MARROW DATA & PROBLEMS IN THE PACIFIC REGION.			
F Oct-29-87		# TELEPHONE CALL DR R STEIN, FDA BIOSTATISTICIAN		DJF	871348
		PHONED DR J GOLDBERG RE QUESTIONS ON THE 4-52 BREAST CA REPORT RELATED TO 80 CUTOFF VALUE FOR SGOT & ESTIMATION OF TTD.			
F Oct-30-87		* TELEPHONE CALL DR G BURKE, MRO		DJF	871337
		CALLED DR S MARCUS RE HIS RECENT REQUEST FOR THE MISSING BONE MARROW RATING DATA.			
L Nov-02-87		# RESPONSE TO FDA REPLAC OF APP VI TO 3-603 STUDY REQ BY DR BURKE 10/28/87		DJF	871445

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
		REPLACEMENT OF APP VI OF THE 3-603 STUDY SUBMITTED ON 10/22/87 FILED PER DR BURKE'S REQUEST OF 10/28/87			
L Nov-04-87		CORRESPONDENCE HANDOUTS FOR 12/7-8/87 ONCOLOG ADV COMM MTG (20 CC)	DJF		871413
L Nov-06-87		CORRESPONDENCE REPLACEMENT COPY:APPEND#6 SUB.11/2/87;APPEND#14 SUB.10/22/87	DJF		871417
F Nov-06-87		# TELEPHONE CALL DR D HERSEY, SEC ONCOL DRUGS ADV COMM	DJF		871376
		QUESTIONS FROM ONCOLOGY DIV TO ADVISORY PANEL OBTAINED.			
L Nov-12-87		PERIODIC REPORT 10/1/86 - 9/30/87	AH		880091
L Nov-12-87		# RESPONSE TO FDA LISTING OF LAB CONVERSION FACTORS FILED	DJF		871446
		A LISTING OF LAB CONVERSION FACTORS FOR THE 3-603 STUDY FILED PER DR BURKE'S REQUEST.			
F Nov-13-87		* TELEPHONE CALL DR G BURKE, MRO	DJF		871395
		REQUESTED ADD'L ANALYSES OF SURVIVAL,RR & RESPONSE DURATION FOR INTENT-TO-TREAT PTS(EXCEPT THOSE WRONGLY DIAGNOSED) IN 3-74 & 3-603. ALSO TO RUN SAME DELETING HONG KONG & TAIWAN.			
L Nov-19-87		# TELEPHONE CALL DR G BURKE, MRO	DJF		871431

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DR S MARCUS PHONED RE ERRATA IN THE 3-603 LEUKEMIA STUDY.

F Nov-19-87	#	TELEPHONE CALL DR R STEIN, BIOSTATISTICIAN	DJF	871451
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REQUESTED FROM MR WEISS CALCULATION OF CONFIDENCE LIMITS FROM THE LEUKEMIA STUDIES 3-74 & 3-603.

F Nov-24-87	#	TELEPHONE CALL DR G TURNER, OFFICE OF SCIENTIFIC INVEST	DJF	871439
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REQUESTED 3 VOLUMES FROM 10/2/87 LEUKEMIA SUBMISSION CONTAINING CLINICAL REPORT OF 3-74 STUDY TO AID IN HIS SELECTION OF SITES TO AUDIT

L Nov-24-87	#	CORRESPONDENCE 3-40(BREAST) SUBGROUP ANALYS BASED ON PROG FACTORS	DJF	871448
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AN ANALYSIS OF SURVIVAL DATA FROM THE 3-40 BREAST STUDY WAS SUBMITTED FOR SUBGROUPS BASED ON PROGNOSTIC FACTORS(AS WAS DONE FOR YHE 4-52 STUDY).

L Nov-24-87	#	RESPONSE TO FDA ADD^N SUBSET ANALYS 3-74/3-603 & EVAL OF SUPP CARE 3-603	DJF	871447
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ADD^N SUBSET ANALYSES FOR RESPONSE RATE, SURVIVAL, & RESPONSE DURATION FILED PER DR BURKE,S REQUEST. ALSO AN EVALUATION OF THE QUALITY OF SUPPORTIVE CARE FOR PATIENTS WITH INFECTIONS IN 3-603 WAS PROVIDED.

F Nov-25-87	#	TELEPHONE CALL DR G BURKE, MRO & DR J JOHNSON, GR DIR ONCOL	DJF	871437
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ASKED THAT WE RESTRICT OUR PRESENTATIONS ON LEUKEMIA & BREAST CANCER TO 45 MIN EACH.

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
L Nov-30-87		RESPONSE TO FDA COPIES OF 3-74 VOLS(LEUK) TO DR G TURNER AS REQUESTED		DJF	871440
		(a) CORRESPONDENCE FDA REQ FOR VOL 1,2,3(14.1,14.2,14.3)LEUKEMIA 3-74 STUDY			
L Nov-30-87		# TELEPHONE CALL DR G BURKE, MRO		DJF	871449
		REQUESTED SUPPORTIVE CARE INFO ON PATIENTS WHO DIED DURING CONSOLIDATION THERAPY IN THE 3-74 & 3-603 LEUKEMIA STUDIES. ALSO WANTED HAZARD RATIOS FOR THE 3-603 SUBSET ANALYSES PROVIDED 11/24/87. ASKED THAT WE OFFICIALLY SUBMIT THE BREAST CA SUMMARY SENT TO THE ADVISORY PANEL TO THE NDA.			
L Dec-01-87		CORRESPONDENCE LIST OF LEDERLE PRESENTERS(NOVANTRONE)@ FDA ADV COMM MTG		DJF	871490
L Dec-01-87		# TELEPHONE CALL DR D HERSEY, SEC ONCOL DRUGS ADV COMM		DJF	871453
		DR DEAN BRENNER OF ROSWELL PARK WILL BE THE NEWEST MEMBER OF THE ADVISORY PANEL.			
L Dec-02-87		# TELEPHONE CALL DR G BURKE, MRO		DJF	871454
		DR S MARCUS CALLED ABOUT THE PRESENTATION OF SUPPORTIVE CARE DATA FOR PATIENTS IN THE 3-603 LEUKEMIA STUDY.			
L Dec-03-87		# TELEPHONE CALL DR G BURKE, MRO		DJF	871462
		PROVIDED DR BURKE WITH SURVIVAL HAZARD RATIOS ON SUBGROUPS OF PATIENTS FROM THE 3-603 LEUKEMIA STUDY REQUESTED ON 11/30/87.			

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L Dec-07-87		* MEETING ONCOLOGIC DRUGS ADVISORY COMM MTG LEUKEMIA APPROVED		DJF	871524
		ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING - NOVANTRONE APPROVED 7-2(2 ABSTAINING) FOR FIRST-LINE USE IN COMBO VS ANLL. 11-0 VOTE AGAINST ITS USE AS SINGLE USE IN RELAPSED ANLL. USE IN BREAST CANCER NOT APPROVED BY AN 8-3 VOTE.			
F Dec-08-87		# MEETING DR G TURNER, OFFICE OF SCIENTIFIC INVESTIGATION		DJF	871508
L Dec-09-87		* RESPONSE TO FDA		DJF	871520
		(a) CASE REPORT FORM RANDOM CRFs FROM #3-74 REQ BY DR G TURNER(FDA)FOR AUDITING		/003-074-0	
F Dec-09-87		# TELEPHONE CALL DR G BURKE, MRO		DJF	871527
		CALLED DR MARCUS RE WORDING OF THE PI RELATED TO THE CONSOLIDATION PHASE OF TREATMENT AND LISTING OF ADRS FOR THE INDUCTION PHASE IN STUDY 3-74.			
L Dec-10-87	F Oct-16-87	RESPONSE TO FDA WE AGREE TO REQUESTED MODIFICATIONS TO ANALYTICAL TESTING		GRP	880030
L Dec-10-87		* RESPONSE TO FDA DRAFT LABELING FOR USE IN LEUKEMIA		DJF	871521
		(a) LABEL,DRAFT,PACKAGE INSERT PROP.DRAFTLABEL FOR ANLL + ADV REAC LIST(3=74/3-603)DR.BURKE			
		DRAFT LABELING FOR USE IN ANLL REFLECTING SEVERAL CONVERSATIONS WITH DR G BURKE WERE SUBMITTED TO FDA ALONG WITH A WANG DISKETTE.			

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L Dec-10-87	F Oct-16-87	# CORRESPONDENCE WE AGREE TO SUGGESTED ANALYTICAL MODIFICATIONS		GRP	880013
F Dec-11-87		# TELEPHONE CALL DR G BURKE, MRO		DJF	871528
		<p>CALLED DRS MARCUS AND FOLEY SEVERAL TIMES RE THE FINAL LABELING FOR USE IN ANLL. FDA HAS MADE A NUMBER OF REVISIONS TO OUR PROPOSED TEXT SUBMITTED EARLIER IN THE DAY EG THE PK SECTION AND THAT DEALING WITH CARDIOTOXICITY.</p>			
F Dec-14-87		* MEETING DR G BURKE, MRO & MS A SINDELAR,CSO		DJF	871539
		<p>DRS CARTWRIGHT & SALETAN WERE ASKED TO STOP OFF AT THE ONCOLOGY DIV TO DISCUSS REVISIONS TO OUR PROPOSED PI SUBMITTED ON 12/11/87. AGREEMENT WAS REACHED ON REVISIONS.</p>			
F Dec-15-87		* TELEPHONE CALL MS A SINDELAR, CSO		DJF	871540
		<p>CALLED TO INDICATE TWO ADDITIONAL CHANGES TO PI RE SINGLE DOSE USE AND CHANGE OF LABEL FROM "FOR INJECTION" TO "INJECTION". WE EXPRESSED OUR OBJECTIONS TO THE LATTER REVISION FROM A SAFETY VIEWPOINT.</p>			
F Dec-23-87		* APPROVAL APPROVAL FOR INITIAL RX OF ANLL IN COMBINATION		DJF	880009
L Dec-30-87		# TELEPHONE CALL MR K FEATHER, DIR DIV DRUG ADVERTISING		NAS	880007

APPROVED TRADEMARK NOVANTRONE MITOXANTRONE HCL
FOR PRE-LAUNCH REMINDER AD.

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19-297	NDA	NOVANTRONE *MITOXANTRONE INJ			
L Jan-04-88		# TELEPHONE CALL MS A SINDELAR, CSO		DJF	880008
		REVISED ADR TABLE AGREED TO FOR FINAL PRINTED LABELING.			
F Jan-12-88	L Jan-05-88	* ACKNOWLEDGEMENT FDA ACKNOWLEDGES RECEIPT OF SUPP 1/12/88	S001	GRP S001-RCPT DATE	880132
L Jan-20-88	L Dec-20-87	* SUPPLEMENT SUBMISSION OF PRESERVATIVE EFFICACY FOR MULTIPLE DOSE VIAL		GRP	880135

EXHIBIT D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 4278689
Issued July 14, 1981

Inventors: Keith C. Murdock
Frederick E. Durr

Assignee: AMERICAN CYANAMID COMPANY, One Cyanamid
Plaza, Wayne, New Jersey 07470

Title: 1,4-Bis(Substituted-Amino)-5,8-Dihydroxy-
anthraquinones and Leuco Bases Thereof

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

SIR:

DECLARATION IN SUPPORT OF APPLICATION FOR EXTENSION OF TERM OF U.S. PATENT NO. 4278689

Alphonse R. Noë hereby declares that he is
the Manager of the Patent Law Department of the
AMERICAN CYANAMID COMPANY; and further declares:

THAT by a resolution of the Board of
Directors of the AMERICAN CYANAMID COMPANY (a copy of
which is attached hereto and made a part of this
declaration), he is authorized to execute and file with
the United States Patent and Trademark Office such
documents as he may deem to be necessary from time to
time;

THAT this declaration is in support of and
filed with the accompanying application for extension
of the term of U.S. Patent No. 4278689;

THAT the AMERICAN CYANAMID COMPANY is the
assignee of record of U.S. Patent No. 4278689 by an

assignment recorded at frame 214 of reel 3507 in the United States Patent and Trademark Office;

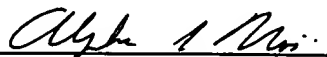
THAT he has reviewed and understands the contents of the accompanying application being submitted pursuant to section D of the GUIDELINES FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 as published in 1047 OG 16-20 (1984);

THAT he verily believes U.S. Patent No. 4278689 is subject to extension pursuant to section A of the hereinabove-identified GUIDELINES;

THAT he verily believes an extension of the length claimed in the accompanying application is fully justified under 35 U.S.C. 156;

THAT he verily believes U.S. Patent No. 4278689 for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in section B of the hereinabove-identified GUIDELINES; and

THAT all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.


Alphonse R. Noë
1937 West Main Street
Stamford, CT 06904-0060
(203)348-7331

EAC/jhr
27962

CERTIFICATE

I, D. C. Droste, Assistant Secretary of American Cyanamid Company, a Maine corporation (the Company), hereby certify that the following is a complete and accurate copy of a resolution duly adopted by the Board of Directors of the Company at a regular meeting held on October 17, 1972, at which meeting a quorum was present and acting throughout, and that the same has not been rescinded or further amended and is now in full force and effect:

RESOLVED: That any one of the Chairman of the Board, the President, the Vice Presidents, the Treasurer, the Assistant Treasurers, the Secretary, the Assistant Secretaries, the Manager of the Patent Law Department, and the Manager of the Trademark Copyright Law Department, be, and he hereby is, authorized, in the name and on behalf of this Company, to execute such powers of attorney and other documents, and to make such affidavits, as the person executing such documents or making such affidavits may deem to be necessary or desirable, from time to time, in connection with Letters Patent or trademark registrations, and applications for Letters Patent or trademark registrations, or in connection with any opposition, nullity, revocation, infringement or cancellation proceedings relating to Letters Patent or trademark registrations and to applications for Letters Patent or trademark registrations of other parties.

I FURTHER CERTIFY that A. R. Noe is Manager of the
Patent Law Department of this Company.

IN WITNESS WHEREOF, I have hereunto set my hand
and affixed the seal of this Company this 1st day of
February, 1988.

A handwritten signature in dark ink, appearing to read "A. R. Noe", is written over a horizontal line.

Assistant Secretary